JOINT ANNUAL MEETING: DUBLIN, JULY 3—11

DO NOT CIRCULATE

UNIVERSITY OF MICHIGAN
JUN 18 1952
MEDICAL LIBRARY

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY MAY 31 1952

TABLE OF CONTENTS

Cortisone in Rheumatic Carditis: Some Preliminary Observations
E. N. Chamberlain, M.D., F.R.C.P., John Duncan Hay, M.D., F.R.C.P., and Denis M. Freeman, M.D., M.R.C.P. 1145

Some Concepts of Rheumatic Disease.—II J. H. Kellgren, M.B., F.R.C.S. 1152

Prevention of Streptomycin Resistance by Combined Chemotherapy
Medical Research Council Investigation 1157

Chemotherapy of Pulmonary Tuberculosis in Young Adults
Marc Daniels, M.R.C.P., D.P.H., and A. Bradford Hill, C.B.E., Ph.D., D.Sc. 1162

Kernicterus Without Prematurity or Blood-group Incompatibility
N. R. Butler, M.D., M.R.C.P., and W. G. Spector, M.B., M.R.C.P. 1168

Study on the A Factor as a Cause of Haemolytic Disease in Premature Babies
Somsak Phansomboon, M.B., and O. J. Pollak, M.D., Ph.D. 1170

Peculiar Syndrome of "Bladder Paralysis" in Natives of South Central Africa
M. Gelfand, M.D., F.R.C.P., and E. E. Barnett, M.B., F.R.C.S.Ed. 1172

Relief of Acute Left Ventricular Failure by "Priscol" David Wheatley, M.D. 1174

MEDICAL MEMORANDA
Case of Ectopia Cordis Surviving Nine Hours. Eleanor J. Wilson, M.B. ..1175
Torsion of a Fallopian Tube. P. G. Seed, M.B., D.R.C.O.G. 1176

REFRESHER COURSE
Rheumatoid Arthritis. W. S. C. Copeman, M.D., F.R.C.P. 1185

GENERAL ARTICLES AND NEWS
Nova et Vetera 1188
Simple Pulse Indicator. V. J. Keating, M.B., D.A. 1188
Reports of Societies 1189
Medical Notes in Parliament 1199
Medico-Legal 1200
Universities and Colleges 1201
Medical News 1203
Births, Marriages, and Deaths 1205
Questions and Comments 1205

REVIEWS
Growth of Towns 1177
Ophthalmological Papers 1177
Life in Harmony 1178
Before and After Marriage 1178
Compelling Genius 1178

Vital Statistics 1202

LEADING ARTICLES
Cortisone in Carditis 1179
Chemotherapy of Tuberculosis 1179

ANNOTATIONS
Charges on Prescriptions 1181
President, 1953–4 1181
Death on the Table 1181
Science in Piccadilly 1182
Contraceptives by Mouth? 1183
Motor-cycle Accidents 1183
Great Ormond Street Centenary 1184
The Stewart Prize 1184

OBITUARY
Laurence Kilroe, M.D. 1197
J. J. K. Pentony, M.B. 1198
John Hare, O.B.E., M.D., F.R.F.P.S. 1198
C. J. Neilan, L.A.H. 1198
Frederick Lace, F.R.C.S. 1198
W. G. Kingston, L.M.S.S.A. 1198
P. A. Steven, M.B. 1199

SUPPLEMENT
Full Contents on First Page of Supplement
Supplementary Annual Report of Council, 1951–2 255
Proceedings of Council 272
Durham Closed Shop 276
Charges to Patients 276

CORRESPONDENCE
Heart Disease Research. W. P. D. Logan, M.D., and J. N. Morris, M.R.C.P. 1190
Hypertension. I. Polunin, D.M.; H. W. Crowe, D.M.; E. Brauer, M.D. 1190
Ethyl Chloride for Unconscious Hysterics. D. Monk Adams, M.B. 1191
Gestation Period. A. B. Partridge, M.A. 1192
Leucotomy. S. A. Gueukdjian, M.D. ..1192
Discharge of Certified Mental Patients. Alexander Walk, M.D.; Aaron Lask, M.R.C.S.; C. A. H. Watts, M.D. 1193
Copper in Foods. G. H. Bourne, D.Phil. 1193
Ulcerative Colitis. Isabel G. Smith, M.B. 1194
Tuberculosis. H. J. Trenchard, M.B., and R. Grenville-Mathers, M.D. 1194
Intra-articular Streptomycin. G. P. Arden, F.R.C.S. 1194
Pneumoencephalography and Fits. A. A. McConnell, F.R.C.S.I. 1194
Skin Banks. H. P. Pickerill, M.S. 1194
Barrier of Silence. Francon Roberts, M.D.; Malcolm Donaldson, F.R.C.S. 1195
Fouling the Nest. E. C. Atkinson, M.B.; Stephen Taylor, M.D. 1195
Damnable Heresy? M. C. Andrews, M.D. 1196
Is Illness Inevitable? B. Lee, M.R.C.S. 1196
Acidosis. F. Charlotte Naish, M.D. ..1196
Trapping the Surgeon's Sweat. A. Dickson Wright, F.R.C.S. 1197

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4769, WEEKLY, PRICE 2/-

Copyright

REGISTERED AS A NEWSPAPER

PERSONAL WEIGHING MACHINE

NO LOOSE WEIGHTS

Capacity 24 stone × 1 oz. divisions.

Hardened steel knife edges and bearings.

Complies with local Weights and Measures regulations.

Finished in white enamel.

Also available

COMBINED BABY & TODDLER WEIGHER

Capacity 60 lb. × ½ oz. divisions. No loose weights.

Extra large perspex Baby Basket.

Hygienic and easy to clean.

Finished in white enamel.

Please send for illustrated leaflet

HERBERT & SONS LTD.

38 CHARTERHOUSE ST., SMITHFIELD, E.C.1

Telephone: Clerkenwell 2812 (6 lines)

ANOTHER RECENT

ACTA

PUBLICATION

FIRST ANNUAL REPORT ON STRESS

SUPPLEMENT TO THE MONOGRAPH "STRESS"

by **HANS SELYE**
M.D., Ph.D. (Prague)
D.Sc. (McGill), F.R.S.(C.)

HIGHLIGHTS OF THE BOOK

★ It deals with current developments in the field of ACTH, Cortisone, STH, and the adaptation syndrome in general.

★ It presents a new unified theory of medicine.

★ It acts as a guide to the entire literature on Stress.

★ It combines an extensive classified index of pertinent facts on the Stress problem and a concise textbook-like evaluation of the principal findings.

★ It marks the start of an annual series of such reports, which will embody the latest developments with ACTH, Cortisone, and STH.

644 pages, numerous illustrations and references.

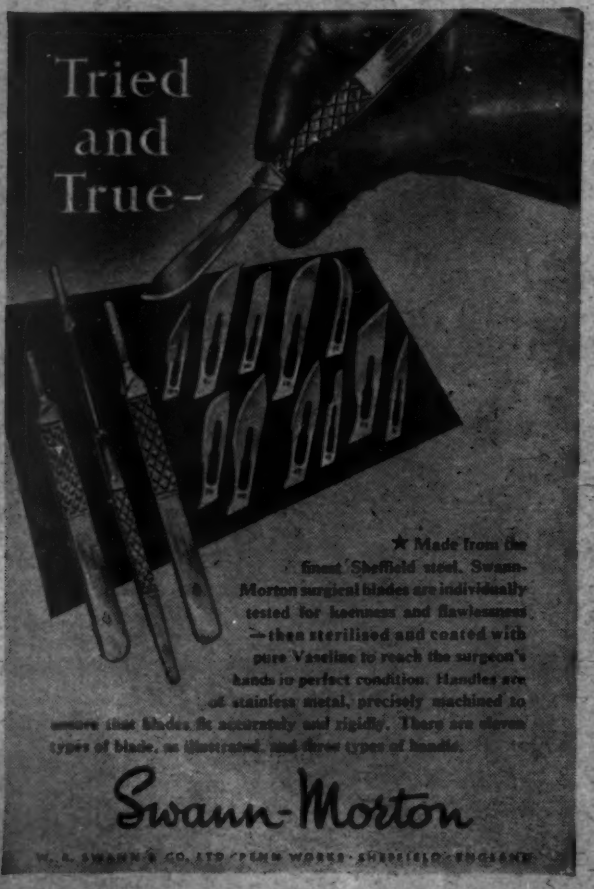
$10.00 plus .34c. postage.

Other books by the same author:

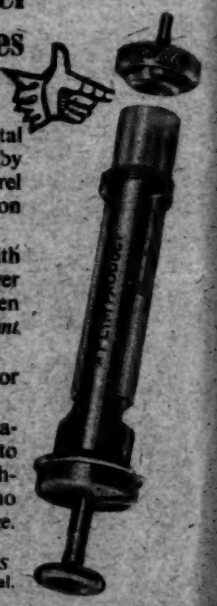
"STRESS"	$14.00 + .48c. postage
"TEXTBOOK OF ENDOCRINOLOGY" ...	12.50 + .44c. "
"OVARIAN TUMOURS"	22.75 + .89c. "

ACTA INC. (Medical Publishers)

5465 Decarie Blvd., Montreal


Tried and True-
★ Made from the finest Sheffield steel, Swann-Morton surgical blades are individually tested for keenness and flawlessness—then sterilised and coated with pure Vaseline to reach the surgeon's hands in perfect condition. Handles are of stainless metal, precisely machined to ensure that blades fit accurately and rigidly. There are eleven types of blade, as illustrated, and three types of handle.
Swann-Morton
W. R. SWANN & CO. LTD. PENN WORKS · SHEFFIELD · ENGLAND

The replaceable barrel means great economies in the long run



The glass barrel is protected by a metal casing and breakage risk is thereby reduced to a minimum. If the glass barrel is broken only the glass barrel and piston need be renewed.

Spare barrels are supplied complete with individually fitted pistons. Users however are advised to order a spare barrel when they buy the syringe; this permits *instant* replacement.

All components can be taken apart or assembled in a few seconds.

No cement or solder is used and sterilization can be done at temperatures up to 200° C. The metal piston must be withdrawn during sterilization but there is no need to dismantle the rest of the syringe.

SIZES: 1, 2, 5, 10 and 20 c.c.

INTERCHANGEABLE NEEDLE FITTINGS
Record, Luer and all other types. Side and central.

PLIM

HYPODERMIC SYRINGES

Obtainable from Surgical Instrument Houses and Chemists

MANUFACTURERS: NORMAN PHETHEAN LTD
CROYDON ROAD · CATERHAM · SURREY
Telephone: Caterham 2460

BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 31 1952

CORTISONE IN RHEUMATIC CARDITIS: SOME PRELIMINARY OBSERVATIONS

BY

E. N. CHAMBERLAIN, M.D., F.R.C.P.
Senior Physician, Royal Southern Hospital and Sefton General Hospital, Liverpool

JOHN DUNCAN HAY, M.D., F.R.C.P.
Physician, Royal Liverpool Children's Hospital

AND

DENIS M. FREEMAN, M.D., M.R.C.P.
Consultant Physician, Warrington General Hospital and Warrington Infirmary

The dramatic and immediate results achieved in the treatment of rheumatoid arthritis by the use of cortisone and A.C.T.H. was followed by observations on other forms of arthritis, among them rheumatic fever.

Several claims have been made for the beneficial influence of these drugs upon the articular manifestations, pyrexia, and raised sedimentation rate found in acute rheumatism. It was naturally hoped that the preparations might exert a beneficial effect upon the cardiac muscle and fibrous valves affected by rheumatic fever similar to that upon the skeletal muscles and fibrous tissue in rheumatoid arthritis. These hopes were expressed by Hench, Slocumb, *et al.* (1949), who treated three cases of rheumatic fever, noting a rapid disappearance of fever, tachycardia, and arthralgia. The E.S.R. became normal within three to four weeks. They further observed electrocardiographic evidence of improvement. Thus the P–R interval, which was prolonged in two cases, returned to normal within a week, and in one case the RS–T and the T wave changes disappeared in 26 days. The clinical manifestations of carditis in their cases do not appear to have been convincing, and the authors were well aware of this though they hoped that cortisone might favourably influence the course of rheumatic carditis. Further, they thought that the effects of cortisone on other manifestations of rheumatic fever were superior to those obtained by salicylates or in cases allowed to run a natural course. Later work by the same authors seemed to support their original claims (Hench, Kendall, *et al.*, 1950).

Barnes and Smith (1950) also treated five cases and noted the disappearance of fever, tachycardia, and joint pains in a few days. They, too, claimed that the P–R interval tended to revert to normal in the first week of treatment and that tachycardia was succeeded by bradycardia, though the latter disappeared on reduction or withdrawal of cortisone. In one of their cases, after two weeks' treatment, there was a disappearance of physical signs upon which a diagnosis of myocarditis, pericarditis, pulmonary congestion, and pleural effusion had been made.

Another interesting case was that described by Bell, Bell, and Wilson (1950) in which severe rheumatic pancarditis with pneumonitis and congestive cardiac failure was treated with the heavy initial dose of 2,000 mg. of cortisone in 48 hours. During this time pericardial friction and gallop rhythm disappeared and the authors did not notice any untoward symptoms from these large doses. There was, however, a recurrence of symptoms on discontinuing the treatment.

Another small group of cases was beneficially treated by McEwen *et al.* (1950), and larger groups are described by Keith and Neill (1951), 23 cases, and by Coste *et al.* (1950), 15 children. Varying degrees of success are claimed.

By contrast Harris *et al.* (1951), whilst admitting the subsidence of other constitutional manifestations of rheumatic fever, found that the cardiological signs showed no improvement throughout the entire period of observation. They treated four cases.

Videbaek *et al.* (1950) also treated three cases without response to high dosage of cortisone, though they claimed improvement with A.C.T.H.

It is evident, therefore, that there is much conflict of opinion about the influence, if any, of cortisone on the cardiac lesions of rheumatic fever. A decision on this matter is of great importance in view of the crippling effects of this disease in childhood, and the fact that hitherto no treatment has been known to modify the course of the carditis, however effective it may have been in controlling other manifestations.

Suitable cases of rheumatic carditis do not occur often enough for any one group of observers to form firm conclusions about the effects of a new remedy. Clinical manifestations and the natural history of rheumatic heart disease probably vary in different climates and at different seasons. The supply of cortisone and A.C.T.H. is still limited.

Final judgment on the value of these preparations in the treatment of rheumatic carditis may therefore have to depend upon a critical comparison of small-scale observations made by different workers. We have

pooled our resources of clinical material as well as the supplies of the drugs issued to us through the Liverpool Regional Hospital Board and the Board of Governors of the United Liverpool Hospitals.

Selection of Cases

Our series included cases admitted direct to the hospitals mentioned in the paper, some having been sent to us through the courtesy of colleagues. Two of us (E. N. C. and D. M. F.) are also responsible for 40 children with rheumatic heart disease in St. Joseph's Heart Hospital, Rainhill, and a selection was made of those considered suitable for cortisone therapy. The cases admitted direct to the Royal Southern and Children's Hospitals were generally those showing a fully developed rheumatic carditis, and, in three, necropsy confirmed the clinical diagnosis. In the other cases the signs of active carditis were less conclusive, but were definite enough to justify treatment. The criteria of active carditis will appear from the description of the individual case, and we are aware of the difficulty of proof of diagnosis in certain instances. We have regarded as proof the presence of pericarditis with friction or effusion when there were other rheumatic manifestations and nothing to suggest a non-rheumatic cause such as pneumonia or tuberculosis. If cardiac signs such as murmurs and enlargement were present in a patient with other rheumatic signs and symptoms, the diagnosis was thought permissible.

A combination of some of the following signs was accepted as evidence of the rheumatic state : rheumatic nodules, articular rheumatism, pyrexia, increased sleeping pulse rate, raised sedimentation rate, and rheumatic rashes.

The value of electrocardiographic studies is dealt with in the discussion.

Many cases at first thought suitable for cortisone therapy were discarded because the signs and symptoms of rheumatic carditis subsided without treatment. After strict selection, therefore, we were left with the cases recorded here, in which all three of us agreed there was justification for regarding the carditis as more or less active.

Observations and Treatment

Our purpose was to determine the effects, if any, of cortisone on rheumatic carditis. Many incidental clinical and laboratory investigations were made. In most cases periodic estimations of the red and white cell count (particularly of the eosinophils), the erythrocyte sedimentation rate, and blood electrolyte values were available. For these we are greatly indebted to the pathologists of our respective hospitals—Dr. St. Hill at the Royal Southern Hospital, Dr. Rewell at the Royal Liverpool Children's Hospital, Dr. Brundret at Sefton General Hospital, and Dr. McGinley at Whiston Hospital.

The cardiovascular observations were generally made by each of us independently, but our findings rarely differed. The size of the heart was determined clinically, as it was not justifiable to allow a child with rheumatic carditis to stand for an accurate teleradiogram. On a few occasions portable radiography was used, more to exclude associated pulmonary lesions than to determine the size of the heart. Change in murmurs was noted from day to day, and according to the intensity of the murmur an empirical classification of apical systolic murmurs into grades 1 to 5 was adopted. Electrocardiographic observations included the standard leads, the unipolar limb leads, and the V leads (2, 4, and 6). Measurements of the P–R and Q–T intervals were nearly all made in standard lead II.

In most cases it was possible to make these investigations once or more often during the control period before the employment of cortisone. We aimed at a minimum of one week for controlled observations before treatment began. In a few cases this was not possible owing to the grave state of the patient on admission. In other cases a much longer period was available before the child was finally selected for treatment. All the cases were in children or adolescents, and the doses of cortisone varied from 50 to 100 mg. daily, spread over periods of ten days to five weeks. In one or two cases larger doses were used. The preparation was "cortone acetate," prepared by Messrs. Merck & Co.

The children were kept under observation for periods of a few weeks to many months, according to the course of the illness.

Case 1

K. O'H. Boy aged 13. (By courtesy of Dr. G. Sanderson.)

History.—February, 1951: appendicectomy; free fluid; no glands; slow recovery. March 6–16: pains in knees and feet and erythematous rash. March 24: severe dyspnoea, irritable unproductive cough aggravating pain in the chest.

Examination on Admission (March 27, 1951).—Pale. Dyspnoea even at rest. Rheumatic nodules on knuckles and left elbow. Erythematous rash fading from trunk. Temperature 100.2° F. (37.9° C.). V.R. 124 to 144. Cardiac impulse 3 in. (7.5 cm.) from midline, forcible and slightly diffuse. Pericardial friction base to apex. Signs of pulmonary consolidation right mid-zone.

Period of Control Observation.—None owing to severity of illness. Before treatment E.S.R. 54 mm., eosinophils 1%.

Period of Cortisone Treatment (March 28 until April 4).—Dosage 100 mg. daily. At first there was a slight improvement in general condition, but this soon worsened. Pericardial friction was unchanged and pulmonary consolidation extended. E.S.R. remained at 52 mm., but there was a slight fall in temperature and heart rate. Only one E.C.G. was taken. QTc interval 0.45. Death on April 4.

Necropsy (Dr. Charles St. Hill).—Severe rheumatic carditis with fibrinous pericarditis but no increase in fluid. Recent vegetations on mitral and aortic valves. Sections showed areas of round-cell infiltration in myocardium but no Aschoff nodules. Greater part of both lungs completely solid but dry.

Conclusions.—Fulminating case of rheumatic carditis uninfluenced by cortisone. Fluid imbalance was present when cortisone was first given and necropsy showed only slight evidence of fluid retention.

Case 2

J. H. Boy aged 13. (By courtesy of Dr. White Jones.)

History.—Ill for three months before admission with anorexia, fatigue, and pains in joints without objective signs. Occasional pyrexia.

Examination on Admission (March 29, 1951).—Pallor. Nodules on occiput only. Slight swelling both knees with effusion into the left. Great pain on movement of left hip. V.R. 120. E.S.R. 33 mm. Pulse collapsing. B.P. 95/40. A.B. not unduly forcible and normal in position. Grade 3 apical systolic murmur; loud long blowing aortic diastolic murmur over base of heart and downwards to left of sternum. Active carditis was thought probable but not proved.

Period of Control Observation (March 29–April 6).—Temperature ranged from 98.4 to 101° F. (36.9 to 38.3° C.). Sleeping pulse rate 90 to 120. E.S.R. 19 to 21 mm. The

joint manifestations continued; no new nodules appeared. A doubtful apical diastolic and a soft aortic systolic murmur appeared. April 3: P–R 0.15, QTc 0.45 April 5: P–R 0.16, QTc 0.44.

Period of Cortisone Treatment (April 7–16).—Dosage: first day 200 mg.; next six days 100 mg.; last six days 50 mg. General improvement, subsidence of joint signs, fall of E.S.R. to 9 mm. and of V.R. to 90 within a week. No significant change in clinical cardiac signs. April 10: P–R 0.13, QTc 0.44. April 13: P–R 0.14, QTc 0.44. Eosinophil count unexpectedly rose during treatment.

Period of Subsequent Observation (April 17–July 22). For four weeks there was general improvement except for a short return of articular rheumatism from April 23 to 28. Sleeping pulse rate ranged from 88 to 110, but E.S.R. gradually rose to 20 mm. Clinical heart signs virtually unchanged. Fullness of the face was noted two weeks after cortisone was discontinued and persisted for 10 days. Condition remained fairly satisfactory until June 21, when pericarditis appeared, followed by congestive heart failure and death on July 22.

Necropsy.—Rheumatic lesions of mitral, tricuspid, and aortic valves with pericardial, pleural, and peritoneal effusions.

Conclusions.—The course of the illness suggests that active carditis was responsible for the final development of cardiac failure. Cortisone controlled the rheumatic manifestations for a few weeks, though it is not certain if it affected the carditis. On the other hand, it was not held responsible for aggravation of the cardiac failure, as this appeared five weeks after the drug was discontinued.

Case 3

E. L. Girl aged 8. (By courtesy of Dr. R. W. Brookfield and Dr. R. R. Hughes.)

History and Examination on Admission (November 30, 1950).—Pains in abdomen, chest, and legs. Loss of weight. Anorexia and nausea for two weeks. Child very ill. Temperature 101.4° F. (38.6° C.), V.R. 186, respirations 76. Rough apical systolic murmur. Signs of consolidation in left lower zone.

Period of Control Observation (November 30–December 8).—The patient was not specially selected for cortisone treatment, but as other measures had failed to influence the illness, which was provisionally diagnosed as acute rheumatic carditis, cortisone was thought worthy of trial. Before cortisone the general condition and cardiac signs remained unchanged. Temperature averaged about 99° F. (37.2° C.), but V.R. ranged from 138 to 156. By December 9 the general condition was deteriorating and cyanosis and hepatic enlargement were noted.

Period of Cortisone Treatment (December 9–January 1).—Dosage: December 9–15, 100 mg. daily; December 16–20, 50 mg.; December 20–January 1, 25 mg. The temperature remained just over normal. The sleeping pulse rate fell to 120–140, but there was no change in the heart signs or general condition. Fluid balance was unsatisfactory, but no record was available for comparison before cortisone was started. December 10: P–R 0.12, QTc 0.42. December 18: P–R 0.14, QTc 0.45. Death occurred on January 1, 1951.

Necropsy (Dr. Charles St. Hill).—Acute rheumatic carditis. Cellular infiltration of myocardium with Aschoff nodules. Vegetations on mitral and aortic valves. Old and new pericarditis. Congestive changes in lungs and liver.

Conclusions.—Cortisone did not modify the course of the disease.

Case 4

M. J. Girl aged 6. (By courtesy of Dr. White Jones.)

History.—Well until one month before admission. Joint pains, fever, and cough appeared, and cardiac enlargement, with a loud apical systolic murmur, was noted. Some improvement occurred with salicylates.

Examination on Admission (June 16, 1951).—Looked ill but good nutrition. Two rheumatic nodules on occiput. No joint manifestations or evidence of cardiac failure. V.R. 125. Cardiac thrust diffuse and turbulent. Grade 4 apical systolic murmur.

Period of Control Observation (June 16–20).—Pending availability of cortisone, salicylates and penicillin were given. In spite of them pyrexia of 100–102° F. (37.8–38.9° C.) continued with raised E.S.R. (22–23) and tachycardia (100–116). No signs of arthritis, or further nodules. Clinical heart signs unaltered. No E.C.G. taken. Signs of mild congestive heart failure and of pulmonary consolidation developed.

Period of Cortisone Treatment (June 20–July 3).—Dosage: First and second days, 500 mg. daily; then four daily doses of 100 mg. and 50 mg. daily for another eight days. Penicillin was continued in view of the uncertain nature of the pulmonary consolidation. Temperature became normal by the third day and E.S.R. fell steadily to 11 mm. on the thirteenth day. Slight initial general improvement was masked by signs of fluid retention, which was treated on the eighth day by mercurials followed by considerable improvement. Chest clear by the eleventh day. Sleeping pulse kept about 90 after third day of treatment. No change in clinical heart signs except disappearance of extrasystoles and less cardiac tumult. June 23: P–R 0.15, QTc 0.42. June 28: P–R 0.16, QTc 0.40. Eosinophils fell from 0.44 to 0.19%.

Period of Subsequent Observation (July 4–September 4).—Four days after cortisone was stopped there was a return of fever, tachycardia, and cardiac tumult, but no arthritis or nodules. Salicylates controlled the temperature but not the heart rate. Signs of heart failure appeared temporarily, but subsided in the second week of this period. Thereafter the condition remained satisfactory for the remaining six weeks in hospital and for four months subsequent to discharge. No significant change in the E.C.G. during this period.

Conclusions.—Evidence pointed to severe active carditis with pneumonic consolidation, not affected by salicylates or penicillin but showing temporary improvement with cortisone and control of water retention. Relapse soon after cessation of cortisone, but, later, spontaneous improvement.

Case 5

J. W. Boy aged 13.

History.—Ten days before admission: tonsillitis followed by articular rheumatism. Four previous attacks of rheumatism since aged 7.

Examination on Admission (April 6, 1951).—Subjective and objective evidence of articular rheumatism. No nodules or rash. Temperature normal. V.R. 100. B.P. 110/50. A.B. diffuse within nipple line. Grade 3 apical systolic murmur. Doubtful apical diastolic.

Period of Control Observation (April 7–19).—Pyrexia at first and development of rheumatic nodules. Further joint involvement and signs of pulmonary consolidation at right base (for which penicillin was used empirically). Later apex beat moved outside nipple line, and pericardial friction developed on April 13, being widespread by April 19. April 17: P–R 0.20, QTc 0.42, low voltage QRS leads I, aVR, aVL, and V_1.

Period of Cortisone Treatment (April 19–29).—First dose 200 mg., 100 mg. daily on 10 subsequent days. Temperature gradually fell to normal; there was much improvement in the general condition and the lung signs diminished, but the E.S.R. did not fall appreciably (23 to 20). The sleeping pulse fell at first, then rose; the cardiac signs remained unchanged. E.C.G. on April 20, 23, and 27: P–R 0.16; QTc 0.41, 0.47, 0.44. The eosinophil count fell. On the eighth day of treatment signs of fluid retention appeared, and for safety cortisone was discontinued on April 29.

Period of Subsequent Observation (April 30–June 21).—The condition worsened on April 30 with increased dyspnoea, increased respiratory rate, and tachycardia (140). Mersalyl with restriction of fluids was prescribed. By May 4 there were no longer any signs of cardiac failure, fluid retention, or active carditis. Pericardial friction had disappeared but murmurs still present. E.C.G. (May 8) T inverted leads I and V_4, P–R 0.14, QTc 0.42. A streptococcal throat infection then occurred, followed by arthritis and nodules but no further cardiac signs. The acute symptoms subsided with penicillin followed by salicylates, which were continued for 13 weeks. By June 21 there was great general improvement, normal E.S.R. and heart rate, but no change in the heart signs. May 22: P–R 0.14, QTc 0.42. June 1: P–R 0.12, QTc 0.41. The child was seen again December, 1951. He was resuming moderate physical activity and no further signs of rheumatism or carditis had occurred.

Conclusions.—Cortisone seemed to have resulted in improvement in general health, but may have contributed to water retention. This was quickly controlled and the evidence of active carditis disappeared coincidently.

Case 6

J. R. Boy aged 16.

History.—February 8, 1951, sore throat, which returned on March 3 accompanied by stiffness in joints and slight pyrexia. Apical systolic murmur noted (Dr. Prideaux).

Examination on Admission (March 21, 1951).—Rather pale and ill. Bilateral effusions in knee-joints.

Period of Control Observation (March 21–27).—Slight pyrexia with normal pulse rate. Signs of articular rheumatism persisted. Clinical evidence of slight cardiac enlargement with Grade 2 apical systolic murmur. Very doubtful apical diastolic. E.S:R. 59 mm. and 50 mm. Water balance normal. P–R 0.16 to 0.18, QTc 0.36 to 0.38.

Period of Cortisone Treatment (March 27 to May 3).—200 mg. followed by 100 mg. daily until April 3, then 50 mg. daily until April 12, a further 100 mg. daily April 13 to 17, 50 mg. daily until April 27, and, finally, 25 mg. until May 3. Within three days pyrexia and joint symptoms subsided and there was much improvement in general condition. E.S.R. fell (Fig. 1). Cardiac signs unchanged though occasionally Carey Coombs murmur was audible, disappearing towards end of treatment. P–R varied from 0.14 to 0.20, and QTc from 0.38 to 0.45. Slight fullness in face and increase in abdominal girth appeared without oedema or disturbance of fluid balance. Articular manifestations recurred with smaller dosage of cortisone, but after second course of higher dosage rheumatic state finally subsided.

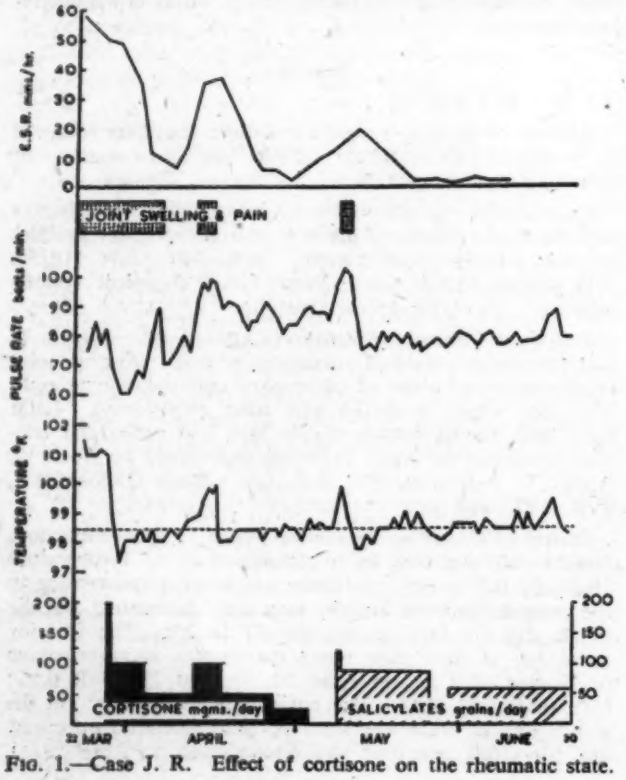


FIG. 1.—Case J. R. Effect of cortisone on the rheumatic state.

Period of Subsequent Observation (May 3 to July 13).—Slight return of articular rheumatism controlled by salicylates; otherwise general improvement. Slight recession in position of cardiac impulse and lessening in intensity of apical systolic murmur. No further diastolic. P–R 0.20, QTc 0.40 (May 10). Continued increase in weight after cortisone, finally reverting to normal proportions in autumn. November, 1951, no evidence of organic valvular lesion.

Conclusions.—Cortisone effected great improvement in rheumatic state, but disappearance of cardiac signs may not have meant more than the coincident decrease in size of left ventricle. The case was interesting in suggesting that increase of weight could be due to obesity rather than fluid retention.

Case 7

D. L. Girl aged 15. (By courtesy of Professor N. B. Capon.)

History.—Tonsillitis four weeks and articular rheumatism four days before admission.

Examination on Admission (April 4, 1951).—Pale, sweating, and temperature 101.8° F. (38.8° C.), acute rheumatism in knees and right ankle. V.R. 80. No cardiac enlargement. No murmurs.

Period of Control Observation (April 4–9).—Temperature varied from 101 to 103° F. (38.3 to 39.4° C.), with E.S.R. 23 to 24 mm. Articular rheumatism moved to elbows, wrists, and other joints. Sleeping pulse rather slower. slight outward movement of cardiac impulse and precordial heaving. Grade 2 apical systolic murmur developed. P–R 0.12, QTc 0.42.

Period of Cortisone Treatment (June 10–24).—Daily dosage 200 mg. for two days, 100 mg. for eleven days, and 50 mg. for another two days. Much general improvement with subsidence of fever and articular signs within a week. E.S.R. fell from 24 to 14. Sleeping pulse from 88 to 44. Cardiac impulse receded slightly but murmurs were unchanged. June 21: P–R 0.14, QTc 0.42.

Period of Subsequent Observation (June 25 to November 26).—Improvement continued for one week; then recurrence of articular rheumatism but no fresh cardiac signs. Apical systolic murmur had disappeared. Condition controlled in a few days by salicylates. In the next four months child remained well except for minor febrile episodes, but soft aortic diastolic murmur appeared in August.

Conclusions.—Cortisone benefited the rheumatic fever and possibly the cardiac changes at first but did not prevent the subsequent development of slight aortic incompetence.

Case 8

S. B. Girl aged 11.

History.—Under observation St. Joseph's Heart Hospital one year. Poor general condition, moderately loud apical systolic murmur and doubtful apical diastolic. May, 1950: severe rheumatic fever with pericarditis followed by mild congestive heart failure. Aortic diastolic murmur noted August, 1950. Then improvement. Recurrence of rheumatic state February, 1951, but no fresh heart signs.

Examination on Admission (February 5, 1951).—Signs of mitral and aortic disease unchanged. No evidence of failure. Pallor, tachycardia, and E.S.R. 17 mm.

Period of Control Observation (February 5–14).—Signs of active rheumatic process gradually subsiding. Cardiac murmurs unchanged. February 12: P–R 0.16, QTc 0.45.

Period of Cortisone Treatment (February 14–24).—First dose 100 mg., subsequently 50 mg. daily. No change in cardiac signs or E.C.G. measurements.

Period of Subsequent Observation.—February 24 to March 20: condition unchanged. March 20, 1951, to March, 1952: general condition at first good with heart signs unchanged, but for the last few months tendency to tachycardia without any fresh rheumatic or cardiac manifestations.

Conclusions.—The carditis in this case, though originally severe, was mild when cortisone therapy was started. The treatment did not modify the condition or arrest the progress of the cardiac signs. The small doses used did not modify body contour or lead to water retention.

Case 9

K. G. J. Boy aged 10. (By courtesy of Dr. Angelman.)

History.—Warrington General Hospital, February 22 to March 28, 1951, with rheumatic fever, apical systolic and doubtful diastolic murmur, and rheumatic nodules. Transferred to Royal Southern Hospital.

Examination on Admission (March 28, 1951).—A few nodules still present. Grade 3 apical systolic murmur. Doubtful apical diastolic.

Period of Control Observation (March 26 to April 12).—Temperature slightly raised at first, falling later. E.S.R. 47–48 mm. initially, falling to 20 later. Cardiac signs unchanged though the diastolic murmur became more obvious. P–R 0.13 to 0.14, QTc 0.41 to 0.44.

Period of Cortisone Treatment (April 13–26).—Seven daily doses of 100 mg., followed by seven of 50 mg. No pyrexia (already normal in control period). Sleeping pulse gradually fell from 100 to 60. E.S.R. fell to 8 mm. after cortisone ceased. No appreciable change in cardiac signs. P–R 0.12, QTc 0.42 and 0.38. Water balance normal; voracious appetite and increase in weight.

Period of Subsequent Observation.—Four days after cortisone was discontinued, reactivity of rheumatic state with pyrexia, tachycardia, and rise of E.S.R. Apical systolic murmur grades 3 to 4. Doubtful short presystolic murmur. May 3: P–R 0.12, QTc 0.42. Child seen several times between May and October, 1951. No further rheumatic manifestations, and heart signs unchanged.

Conclusions.—Clear rheumatic fever but cardiac signs probably subsiding at time of cortisone therapy. No alteration in heart signs under treatment, except bradycardia.

Case 10

V. P. Girl aged 10. (By courtesy of Dr. White Jones.)

History.—Articular pains and listlessness December, 1950, for two weeks. Then well for two months.

Examination on Admission (March 2, 1951).—Rather frail child; temperature 99° F. (37.2° C.); two small nodules on occiput. Joints normal. E.S.R. 20. V.R. 88. Slight cardiac enlargement. Blowing apical systolic and apical diastolic murmurs, also faint aortic diastolic to left of sternum. B.P. 135/58. P–R 0.16, QTc 0.40.

Period of Control Observation (March 3–14).—No manifestations of rheumatism. E.S.R. fell from 20 to 17. No change in cardiac signs. Slight rise in QTc to 0.46.

Period of Cortisone Treatment (March 15–26).—First day 200 mg.; subsequently 100 mg. daily. E.S.R. fell further to 11. No change in cardiac signs, except slight recession of apex. QTc 0.365.

Period of Subsequent Observation (March 27 to December 7).—General condition remained good. Occasional slight pyrexia and rise of E.S.R. to 18 on April 5. Cardiac murmurs unchanged.

Conclusions.—General improvement with fall in E.S.R. but no definite change in cardiac state under influence of cortisone.

Case 11

E. H. Girl aged 14.

History.—Three attacks of tonsillitis, December, 1950, to February, 1951. Two weeks after the last fever and articular rheumatism.

Examination on Admission (March 21, 1951).—Temperature 100.2° F. (37.9° C.). Tonsils large, not obviously infected. Rheumatic nodules on hands, scapula, and occiput. Objective evidence of articular rheumatism, ankles, hands, and wrists. Sleeping pulse 100. No cardiac enlargement. Soft apical systolic murmur (grade 1). P–R 0.2, QTc 0.43. QRS low voltage lead I and AVL.

Period of Control Observation (March 21–April 2).—Pyrexia and joint manifestations subsided but several fresh nodules appeared. Sleeping pulse tended to fall, averaging 82 on last four nights. No further cardiac signs. P–R 0.16, QTc 0.40. E.S.R. readings 17–20 mm.

Period of Cortisone Treatment (April 3–17).—Initial dose 200 mg. followed by 100 mg. daily for 14 days. Temperature never above 99° F. (37.2° C.). E.S.R. fell to 9. Nodules became smaller. Sleeping pulse averaged 52 in second week. Heart signs unchanged. E.C.G. increased voltage in lead I; QTc 0.39.

Period of Subsequent Observation (April 18–November 15).—Condition satisfactory until further tonsillitis April 27. Some joint pains but no further objective signs. No change in heart but new nodules appeared on May 5 and 7. Thereafter satisfactory progress.

Conclusions.—Cortisone accompanied by general improvement and fall in E.S.R. and lessening in nodules. No clear proof of carditis in this case.

Case 12

A. M. Boy aged 8. (By courtesy of Dr. White Jones and Professor N. B. Capon.)

History.—Fever and articular rheumatism 18 days before admission. Partial response to calcium aspirin. Erythema marginatum developed on legs.

Examination on Admission (May 7, 1951).—Objective signs of articular rheumatism still present. Some muscular wasting. V.R. 128. No cardiac enlargement. Apical systolic murmur grade 1–2. B.P. 115/55.

Period of Control Observation (May 7–13).—Pyrexia subsided to 99° F. (37.2° C.), but rheumatism in knees remained unchanged. E.S.R. on several occasions 23. Sleeping pulse fell slightly. Cardiac signs unchanged. P–R 0.12, QTc 0.42. Doubt existed whether the diagnosis was early Still's disease or rheumatic fever. Evidence of cardiac involvement very doubtful.

Period of Cortisone Treatment (May 14–27).—First had 200 mg., next seven days 100 mg., and last six days 50 mg. daily. Temperature normal May 15 and thereafter. E.S.R. fell to 10. Rapid improvement in joints, but left knee-joint remained enlarged and limited in movement. Much improvement in general condition. Sleeping pulse averaged 75 during second week of treatment. No alteration in cardiac state. QTc increased to 0.45, 0.445, and 0.45 in successive records. After eight days' treatment some evidence of fluid retention, which decreased with lessened dose of cortisone. Appetite always good but ravenous during treatment. Gain in weight maintained for three weeks after cessation of cortisone.

Period of Subsequent Observation (May 29–November 22).—After withdrawal of cortisone there was a return of articular rheumatism, pyrexia, and a rise in E.S.R. The apex beat appeared to have moved out slightly. Heart sounds unaltered. QTc 0.425. Salicylates were thereafter employed with considerable improvement. Cardiac murmur and evidence of enlargement disappeared after four weeks. P–R 0.14, QTc 0.42 and 0.43.

Conclusions.—Case finally accepted as one of Still's disease. Joint manifestations and general condition improved by cortisone. No alteration in state of heart.

Discussion of Results

For analysis of the results it seems necessary to separate those severe cases of undoubted carditis from those in which

the cardiac signs were less convincing though there may have been clear evidence of a rheumatic state. The 12 cases which received treatment can be divided into two groups—five in which the lesion was severe (three fatal), and seven in which rheumatic fever with probable involvement of the heart was present in a milder form.

The term "rheumatic fever" is used as being synonymous with the rheumatic state—that is, to include manifestations such as fever with articular involvement, subcutaneous nodules, or rheumatic rashes. It was hoped that the less severe cases might give important information about the optimum dosage of cortisone, for in the severe cases it seemed that large doses were most likely to be effective. Further, we were anxious to find not only whether cortisone would arrest a fulminating type of carditis but also whether it would modify the course in cases of grumbling infection.

In determining the beneficial effects of any treatment difficulty is encountered because of our imperfect knowledge of the natural history of rheumatic fever and especially of rheumatic carditis. Such a sign as pericardial friction is well known to last for days or weeks, or to be completely absent in a case which subsequently proves at necropsy to have extensive pericarditis. Similarly, rheumatic nodules may last a few days only, or may be present for many weeks, and it is sometimes difficult to determine which are new and which are old. Murmurs are notoriously inconstant and are modified by fever, tachycardia, and cardiac dilatation, all of which may wax and wane. The erythrocyte sedimentation rate provides a useful indicator of the course of the rheumatic state, always assuming that non-rheumatic causes for its rise can be excluded.

In assessing these physical signs, therefore, it would be unjustifiable to conclude that *minor* variations in them had any great significance.

The electrocardiographic studies might be expected to give more precise evidence of myocardial involvement. In our experience the information yielded was disappointing. With a clear clinical picture of active rheumatic carditis it is common to have a normal electrocardiogram, and even when the P–R or Q–T interval is lengthened it is not always evidence of myocardial disease. Further investigations on Q–T measurements are necessary before assessing the value of this measurement in active carditis.

Fox *et al.* (1950), for example, observed the phenomenon rather frequently in childhood tuberculosis, and, though Craige *et al.* (1950) noted that the Q–T interval was above the average normal in 29 cases of fatal pancarditis, the level reached was not above the upper limits of normal, and, while generally the changes in the Q–T interval and clinical manifestations of rheumatic fever ran parallel, there were some instances in which they took opposite directions. On the other hand, Taram and Szilagyi (1951), in a large series of cases, found a close relationship between the length of the Q–T interval and the extent of the cardiac disability.

Thus it is clear that an appropriate grouping of signs is necessary before the diagnosis is established, and that physicians may vary to some extent regarding the combination of signs by which they justify the diagnosis. In order that readers may be familiar with the signs which we ourselves have accepted, it was thought advisable to summarize each individual case. Once the pattern of rheumatic carditis has been agreed upon, modifications in that pattern may be regarded as the result of treatment if they were not likely to have occurred in the same period of time without therapy.

In our series two of the rapidly fatal cases showed no appreciable change in the cardiac state during the use of cortisone, nor was there any certain evidence that the drug worsened the condition. It may well have been that such fulminating cases could scarcely have been expected to respond to any form of therapy, and that, on the other hand, the short duration of the illness made it impossible to determine whether cortisone had any ill effects. In one of the fatal cases (No. 1) clinical evidence of pulmonary consolidation was present and the possibility of pulmonary oedema precipitated or aggravated by cortisone was considered, but at necropsy the lungs proved to be quite dry.

In another fatal case (No. 2) there was some improvement in the general condition and articular rheumatism but no material alteration in the cardiac signs. It was clear from the progression of the illness through the stage of congestive heart failure to death, after the cessation of cortisone administration, that the cortisone did not arrest the activity of the carditis which was held to be responsible. Again, it seems improbable that the cardiac failure was precipitated by cortisone therapy in view of the time of its appearance.

In contrast with the fatal cases two others of considerable severity still survive. In Case 4 the diagnosis of carditis was complicated by pneumonia, which was treated with penicillin during the period of control observation. During the same period signs of mild congestive heart failure also appeared. In view of the beneficial results claimed by Bell *et al.* (1950) (in a similar case) for large initial doses of cortisone, two daily doses of 500 mg. were given, followed by lessening doses for 12 days. There was some initial general improvement, but this was masked by water retention, which was controlled by mercurial injections. When the cortisone was discontinued pyrexia returned with a high sleeping pulse rate and cardiac tumult which were unmodified by administration of salicylates.

Case 5 presented somewhat similar features. These two cases illustrate the risk of water retention when cortisone is used in cases with severe carditis, though it would appear that this adverse effect can be controlled by mercurial diuretics. The improvement in the general condition in such cases does not of course indicate any alteration in the carditis, but it may help to sustain the patient over a period of danger. In order to produce even this limited effect, however, it is clear that a careful balance must be maintained between the dosage of cortisone and the use of mercurial diuretics if water retention becomes apparent.

Any improvement recorded had only a brief duration after the cortisone was discontinued, but it is possible that this disadvantage may be overcome by the use of cortisone in smaller doses and over a much longer period. Prolonged administration would probably require periodic diuresis by mercurials and avoidance of dangerous disturbances of the blood electrolytes.

Amongst the milder cases treated there was a general tendency to physical improvement, but in no case were the heart signs conclusively modified.

In Case 6, which was under prolonged observation, it was evident that while a dose of 100 mg. of cortisone daily was adequate to control the fever and joint manifestations and reduce the E.S.R., 50 mg. daily was unable to achieve this. This case also formed an interesting contrast with Cases 2 and 4, in which water retention occurred. The boy developed the same puffiness of the face and increased in weight, but there was no significant change in the fluid balance, and as time passed the texture of the subcutaneous tissues suggested there was an increase in fat.

In this and other cases a voracious appetite during the administration of cortisone disappeared a week or two after the drug was stopped. It seemed reasonable to assume that the increase in weight was partly due to this fact and that it would not be justifiable to conclude that facial swelling and increasing weight were always evidence of water retention.

When the individual signs are compared during the control and cortisone periods the following points emerge:

1. *Cardiac Signs.*—There were no modifications in the heart signs which could be regarded as *conclusive* evidence of benefit from the drug, though in Cases 2 and 6 apical

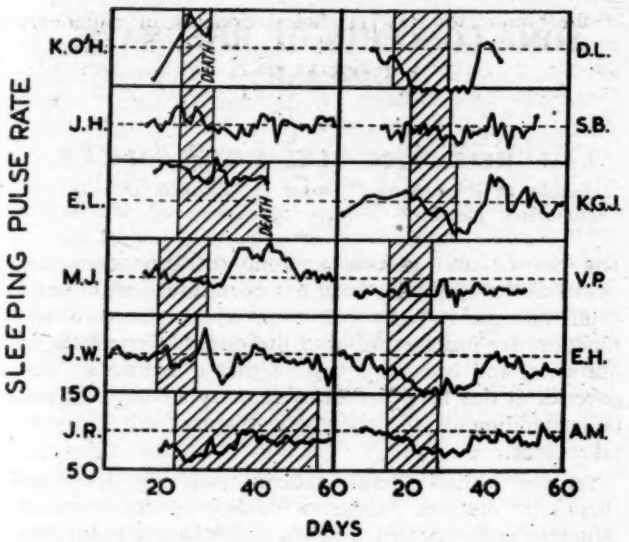


FIG. 2.—Effect of cortisone on sleep pulse rate in active carditis. Shaded areas indicate period of cortisone administration. (In Case J. R. only the average pulse rate was available.)

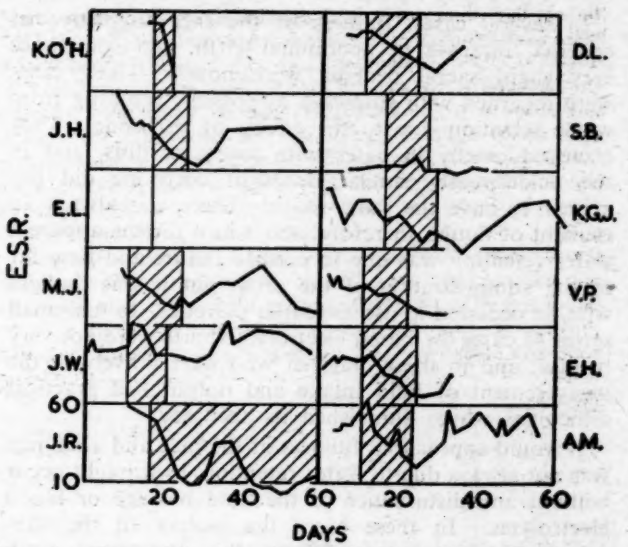


FIG. 3.—Effect of cortisone on erythrocyte sedimentation rate in active carditis. As the micro-method only was available in certain cases, and in the others estimation was made by Wintrobe's method, the Wintrobe figures have been regarded as equivalent to twice the micro-method values. Shaded areas indicate the period of cortisone administration.

systolic murmurs became less intense and diastolic murmurs, probably of the Carey Coombs type, disappeared or became less evident.

2. *Heart Rate.*—There was a clear fall in the heart rate in several cases, sometimes independent of, or greater than, any fall in temperature. This is shown clearly in Fig. 2, and is especially pronounced in Case 7, in which the rate fell to levels below 50.

3. *E.C.G. Changes.*—The P–R interval varied in the control period from 0.12 to 0.19 and during the period of cortisone treatment from 0.12 to 0.18. These quite wide variations gave little justification for assuming in the individual cases that cortisone modified this measurement. In three of the cases the P–R interval shortened during treatment, but in two cases it lengthened. Similarly, the QTc varied from 0.36 to 0.44 during the control period, and during cortisone administration from 0.40 to 0.45. In one case (No. 8) the QTc fell from 0.44 to 0.42 during treatment and rose subsequently to 0.43, but in Case 6 the measurement actually increased during cortisone therapy from 0.36 to 0.41, falling to 0.40 when treatment was discontinued. None of these electrocardiographic changes can therefore be considered of proved importance.

Effect of Cortisone on P–R and QTc Intervals

P–R Interval				QTc Interval			
Case	Control Period	Cortisone Administration	Subsequent Observation	Case	Control Period	Cortisone Administration	Subsequent Observation
K. G. J.	0·135	0·12	0·12	K. G. J.	0·43	0·41	0·40
S. B.	0·160	0·16	0·16	S. B.	0·45	0·425	0·43
K. O'H.	—	0·18	—	K. O'H.	—	0·45	—
E. L.	0·12	0·14	—	E. L.	0·42	0·45	—
J. R.	0·16	0·16	0·20	J. R.	0·36	0·41	0·40
J. H.	0·155	0·135	0·14	J. H.	0·44	0·44	0·44
D. L.	0·12	0·14	0·13	D. L.	0·42	0·42	0·395
J. W.	—	0·18	0·14	J. W.	—	0·43	0·43
E. H.	0·19	0·16	—	E. H.	0·41	0·41	—
V. P.	0·16	0·16	0·16	V. P.	0·415	0·41	0·40
A. M.	0·12	0·12	0·12	A. M.	0·42	0·45	0·44
M. J.	—	0·16	0·13	M. J.	—	0·41	0·4000

4. *Erythrocyte Sedimentation Rate.*—This was estimated when possible by Wintrobe's method, but it was often necessary to use the micro-method, and the figure was doubled for rough comparison with the macro-method. All figures in the text are micro-method unless specified. Fig. 3 shows distinctly that the sedimentation rate falls in a considerable percentage of cases during cortisone administration. But without corresponding improvement in cardiac signs this cannot be held to mean more than the lessening of an infective process, in these cases the rheumatic state.

5. *Eosinophil Count.*—The fall in the eosinophils has no particular significance in relation to rheumatic carditis, but the count was important as a control observation to make sure that the drug was active. Although a fall was not constant, we were satisfied that it occurred often enough on use of the same batch of cortisone.

6. *Improvement in the General State of Health.*—This was observed in several cases, even at times in the very severe forms of the disease. The improvement took the form of increased appetite, liveliness, a better colour, and better sleep. These beneficial signs were in some instances accompanied by disappearance of the articular manifestations and less certainly in the regression of rheumatic nodules. If general ill-health is an important clinical aspect of the rheumatic state, benefit may reasonably be claimed for the cortisone in this direction.

Summary

Twelve cases of rheumatic carditis, all in children, were treated with cortisone. In one the diagnosis was later revised to Still's disease, but as there was some doubt about the presence of carditis treatment was continued.

Three cases were fatal. Two were fulminating in character and the diagnosis of active rheumatic carditis was confirmed at necropsy. Cortisone was tried as a life-saving measure but without success. The third case showed some temporary improvement in the general condition, but cardiac failure and death followed two months later.

The other nine cases showed some evidence of carditis, varying from severe to mild. In none of them was there clear evidence of improvement in the cardiac signs, either clinical or electrocardiographic.

Except in the fatal cases there was usually some improvement in the general condition. The patient's mental well-being improved, as also did the skin colour and appetite. Most notable, however, was the tendency for the heart rate to slow, sometimes irrespective of a fall in temperature.

In several cases, fullness of the face suggestive of oedema, increase in abdominal girth, and sometimes very slight sacral oedema were noted. These cases were regarded with suspicion as possibly resulting from water retention due to the effects of cortisone. They occurred chiefly in cases with severe carditis, and in the milder cases similar doses of cortisone did not appear to have the same result. There was always an element of doubt, therefore, about how far the apparent water retention was due to cardiac failure and how far to the administration of the drug, but it was thought wise on occasion to use mercurial diuretics. In this small series of cases the blood electrolyte values were not very helpful, and in those children who were gravely ill the measurement of fluid intake and output had practical difficulties which diminished its accuracy.

It would appear that fullness of the face and abdomen was not always due to water retention, as it might occur without any disturbance of the fluid balance or blood electrolytes. In these cases the texture of the subcutaneous tissues, particularly the abdominal wall, suggested increased deposition of fat and was often associated with a voracious appetite, during and for some time after cortisone administration.

The investigations confirmed the results of other workers—that cortisone exerts a beneficial effect upon non-cardiac manifestations of rheumatic fever—for example, pyrexia, raised sedimentation rate, and articular inflammation—though it is doubtful if the joints respond more favourably than to salicylates.

The dosage of cortisone varied from 50 mg. to 500 mg. daily over periods of a few days to a few weeks. A fall in the eosinophil count was taken as evidence that the particular batch of cortisone was active.

The results of cortisone treatment were, on the whole, disappointing, and high dosage did not appear to achieve anything more than moderate dosage and carried with it a greater risk of side-effects. Whilst admitting the lack of any spectacular response, we think that the improvement in the patient's general condition and the tendency to slowing of the heart justify further investigation. It would appear that more information is necessary about the effects of prolonged administration of small doses, particularly if there is an initial beneficial response to moderate doses. Such treatment would obviously need careful supervision, cautious dosage, and the use of mercurial diuretics from time to time, if necessary.

We wish to express our appreciation of the help from our colleagues, both medical and nursing. In particular we would like to thank our medical registrars—Dr. McKendrick, Dr. Anderton, Dr. Jones, Dr. Ellenbogen, and Dr. Coulshed—and the resident medical officers of our various hospitals. For electrocardiographic records we are indebted to the careful work of Mr. E. Caldwell.

NOTE.—The case histories, in fuller and more detailed form, will be available on duplicated sheets from the office of the *British Medical Journal* to those who express a special interest in having them.

REFERENCES

Barnes, A. R., and Smith, H. L. (1950). *Med. Conc. cardio-vasc. Dis.*, 19, 59.
Bell, G. I., Bell, R. E., and Wilson, D. R. (1950). *Canad. med. Ass. J.*, 63, 63.
Coste, F., *et al.* (1950). *Bull. Soc. méd. Hôp. Paris*, 66, 1577.
Craige, E., *et al.* (1950). *Circulation*, 1, 1338.
Fox, T. T., *et al.* (1950). Ibid., 1, 1184.
Harris, T. N., *et al.* (1951). Ibid., 3, 215.
Hench, P. S., Kendall, E. C., *et al.* (1950). *Arch. intern. Med.*, 85, 545.
—— Slocumb, C. H., *et al.* (1949). *Proc. Mayo Clin.*, 24, 277.
Keith, John D., and Neill, C. A. (1951). *Canad. med. Ass. J.*, 64, 193.
McEwen, C., *et al.* (1950). *Bull. N.Y. Acad. Med.*, 26, 212.
Taram, L. M., and Szilagyi, N. (1951). *Brit. Heart J.*, 13, 10.
Videbaek, A., *et al.* (1950). *Acta endocrinol.*, 4, 245.

SOME CONCEPTS OF RHEUMATIC DISEASE*

BY

J. H. KELLGREN, M.B., F.R.C.S., M.R.C.P.

Reader in Rheumatic Diseases and Clinical Director, Rheumatism Research Centre, University of Manchester

The normal and morbid anatomy of the connective tissues at the molecular level has been discussed in some detail because it is at this level, where structure and function are inseparable, that the essential processes of life arise, and because I believe that it is through discoveries at this level that revolutionary advances in our understanding of the rheumatic diseases are likely to take place.

At the clinical level patients suffering from the rheumatic diseases present a variety of disorders of structure and function, and we will now examine some of these disorders more closely to see whether or not they can be fitted into a concept of rheumatic diseases based upon the assumption that these diseases result from primary connective-tissue lesions.

Some of the most prominent features of two typical rheumatic diseases, such as rheumatoid arthritis and degenerative joint disease, are set out in Table I. The

TABLE I

Clinical Features	Rheumatoid Disease	Degenerative Joint Disease
Connective tissue lesions	Widespread, often symmetrical, affecting joints, tendons, bones, muscles, skin, viscera, eyes, and other structures. Resulting in marked atrophy and destruction of all affected structures	Often localized to one or more joints, resulting in loss of cartilage and bone in pressure zones with marginal overgrowth
Serum factor agglutinating sensitized sheep cells	Present in high titre in most cases	No more than normal
Loss of body weight ..	Marked, particularly during exacerbations of disease	None
Inflammatory reaction	Marked, both locally in connective tissues as well as systemically	Very little if at all, and only locally in joints
Lymphadenopathy ..	Frequent, particularly in young subjects; occasional splenomegaly	None
Anaemia	Frequent, particularly during exacerbation of disease	,,
Personality changes ..	Frequent during exacerbation of disease	,,
Increased sweating and peripheral vascular disorders	Marked, particularly during exacerbation of disease	,,
Course of disease ..	Very variable with many unexpected exacerbations and remissions	Usually slowly progressive

clinical features of degenerative joint disease clearly result from the initial cartilage lesion, but the manifold features of rheumatoid disease present a more complex problem. But before discussing the various features of rheumatoid disease it would be as well to define this clinico-pathological entity. In many countries, and particularly in America, the term has been used to embrace all forms of polyarthritis of obscure aetiology, so including ankylosing spondylitis, psoriatic arthropathy, Reiter's disease, and many other polyarthritic syndromes, as well as the classical form of rheumatoid disease with symmetrical peripheral joint involvement, widespread soft-tissue changes, and other features mentioned in Table I.

*The second Goulstonian Lecture, given at the Royal College of Physicians of London on January 17. The first lecture was published in our previous issue.

In this country ankylosing spondylitis has always been recognized as a separate disease. Reiter's disease is also distinguished from rheumatoid arthritis by its clinical features and definite epidemiology (Paronen, 1948). Psoriatic arthropathy also has distinctive clinical features and is often diagnosed as such, but after eliminating typical examples of these three well-defined conditions from the rheumatoid group we are still left with a mass of polyarthritic and other diseases which does not present an altogether homogeneous picture and which is very likely made up of rheumatoid disease proper, together with a number of other as yet undefined arthritic syndromes and atypical examples of those that we have already defined. In our unit we have always tried to separate as many as possible of the "atypical" cases from the main group of rheumatoid disease, and the recent clearer definition of the clinical features of primary generalized osteoarthritis (Kellgren and Moore, 1952) has undoubtedly helped to remove a number of cases which might previously have been placed in the rheumatoid group. Nevertheless, there are many cases in which no satisfactory diagnosis can be made on clinical grounds, and the introduction of some specific diagnostic aid would be of real help.

The Agglutination Reaction

In 1948 Rose and his co-workers noted that serum from patients with rheumatoid disease agglutinated sensitized sheep cells in a higher dilution than did serum from subjects not suffering from rheumatoid disease. This finding was confirmed by other workers (Sulkin *et al.*, 1949; Jawetz and Hook, 1950). Technical improvements designed to eliminate the effects of heterophil antibody and other sources of error were introduced by Heller, Jacobson, and Kolodny (1949) and by Ball (1950); and since 1949 this test has been used extensively in our unit, the serological test being carried out blindly by Dr. Ball in the laboratory and his results being subsequently compared with the clinical diagnoses made in the wards and out-patient clinics. Between April, 1949, and November, 1950, the test was carried out on serum from 1,943 individuals, and the analysed results are shown in Table II. It will be seen that the incidence of positive reactions was uniformly low, except in the "rheumatoid" group, where it was 47.4%.

TABLE II.—*Results of Agglutination Test in Rheumatoid Arthritis and Other Diseases*

Disease	Total No.	Positive	
		No.	% of Total
Rheumatoid arthritis	642	304	47·4
Ankylosing spondylitis	203	3	1·5
Osteoarthritis	249	8	3·2
Other arthritides	289	19	6·6
Obscure painful states	176	4	2·3
Rheumatic fever and acute and subacute rheumatism	47	0	0
Non-arthritic disease and normal	337	3	0·9
Non-rheumatoid total	1,301	37	2·8

TABLE III.—*Results of Agglutination Test in Various Subgroups of Rheumatoid Arthritis*

Subgroup	Total No.	Positive	
		No.	% of Total
Total	642	304	47·4
Males	178	109	61·2
Females	464	195	42·0
Subcutaneous nodules present	96	77	80·2
No *x*-ray abnormality found	57	12	21·1
Central joints only involved	25	1	4·0
Associated with psoriasis	14	1	7·1

From the clinical standpoint it was recognized that this "rheumatoid" group was unlikely to be homogeneous, and a further analysis of these 642 "rheumatoid" cases is shown in Table III. It will be seen that in cases with subcutaneous nodules, which are indisputable examples of rheumatoid disease, the proportion of positive agglutination reactions is as high as 80%, while in cases of "polyarthritis" associated with psoriasis and in those without involvement of the peripheral joints positive agglutination reactions were only rarely observed.

Table IV represents a further analysis of the cases classed as other arthritides in Table II, and it will be seen that the relatively high proportion of positive reactions in this group is largely due to cases of disseminated lupus erythematosus, scleroderma, and dermatomyositis, and to a few cases in which the diagnosis was uncertain.

TABLE IV.—*Results of Agglutination Test in Various Arthritides*

Clinical Type	Total No.	No. Positive
Indeterminate arthritis	82	4
Disk lesions	51	0
Gout	18	1
"Infective" arthritis	17	2
Shoulder syndromes	13	0
Tuberculous arthritis	12	0
Disseminated lupus erythematosus	10	6
Atypical polyarthritis	9	2
Scleroderma	7	2
Acromegaly	6	0
Intermittent hydrarthrosis	6	0
Reiter's syndrome	5	0
Gonococcal arthritis	4	0
Osteochondritis	4	0
Tuberculosis and rheumatism	4	0
Periarteritis nodosa	3	0
Allergic arthritis	3	1
Hypertrophic pulmonary osteo-arthropathy	3	0
Dermatomyositis	3	1
Syphilitic arthritis	3	0
Erythema nodosum	2	0
Haemarthrosis	1	0
Myelomatosis	1	0
Morquio's syndrome	1	0
Miscellaneous	21	0
Total	289	19

Thus a positive agglutination reaction is usually found in cases of classical rheumatoid arthritis, disseminated lupus erythematosus, and possibly in dermatomyositis and scleroderma—a group of diseases in which the fibrinoid connective-tissue change is characteristically found and in which intermediate and apparently indistinguishable clinical variants are quite common. On the other hand, the agglutination reaction appears to be uniformly negative in rheumatic fever, although fibrinoid change is equally characteristic of this disease. It is, however, by no means certain that the transient fibrinoid of rheumatic fever and the more permanent fibrinoid of the rheumatoid group are in fact identical, and its association with streptococcal infection and its distinct clinical features are excellent reasons for placing rheumatic fever in an entirely separate category. Thus the potential value of the agglutination reaction is its apparent capacity for distinguishing rheumatoid disease from other atypical and as yet undefined polyarthritic syndromes.

Let us now return to the consideration of rheumatoid arthritis, including only those typical cases in which fibrinoid lesions and a positive agglutination reaction are commonly found, and excluding the various atypical polyarthritic syndromes. The following statements about this disease are largely based upon my own personal experience of some 700 cases taken from a total of over 2,000 cases of arthritis of all types seen in this department during the past four years.

Connective-tissue Atrophy and Weight Loss

The fibrinoid lesion of the connective tissues has already been dealt with, but an equally characteristic feature of rheumatoid disease is the widespread atrophy of bone, cartilage, tendon, skin, and other collagenous structures. Indeed,

Goldthwait (1904) was so impressed with this atrophy that he introduced the term "atrophic arthritis." That these atrophic changes are not entirely due to disuse is clear from the fact that they may be seen in symptomless limbs, and in patients who have always been fully employed; and, indeed, the most severe atrophy may be seen in those courageous patients who have continued to live a most active life in spite of severe and widespread disease. In other conditions an inflammatory tissue reaction tends to heal by the formation of new connective tissue, leading to scarring, but in rheumatoid disease inflammatory reactions seem to be followed by loss of tissue substance and further atrophy, so that the supporting structures of the body seem to melt away, giving rise to those pathetic withered limbs which are so characteristic of this disease.

If our interpretation of the fibrinoid lesion is correct the collagen is lost after disintegration of the normal connective-tissue complex; and where a sizable portion of this complex is destroyed an insoluble residue rich in polysaccharides is left behind. But there is no reason why a molecular disintegration should not take place in a widespread manner throughout the connective tissue without the formation of appreciable quantities of residue, and such a process would certainly explain the widespread connective-tissue atrophy. Although this atrophy is usually progressive in rheumatoid arthritis a temporary reduction of body weight amounting to 2 to 3 stone (12.7 to 19.1 kg.) is a common finding in the early stages of the disease, and this may recur with each exacerbation of the rheumatoid process; the patients, however, usually regain their normal body weight during remissions and may even do so in spite of continuing disease. Part of this weight loss is probably due to low food intake resulting from the loss of appetite that accompanies the personality changes, which are discussed later, but attempts to combat it with special diets, forced feeding, insulin, and other means have not proved very effective. Whether the weight loss results from a mobilization of body protein in an attempt to replace the disintegrating collagen or whether it simply represents the excessive catabolic activity which accompanies tissue injury of all kinds is not clear. With the subsidence of the rheumatoid process the metabolic demands appear to be reduced and body fat, muscle, and other proteins which take part in the metabolic pool are rapidly re-formed, but owing to the very slow turnover of connective-tissue collagen re-formation of these tissues is less complete.

The Inflammatory Reaction

The inflammatory reaction, both local and systemic, accounts for many of the most striking symptoms of rheumatoid disease, such as pain, swelling, stiffness, fever, toxaemia, lymphadenopathy, and the plasma protein changes which form the basis of the sedimentation rate and many other tests. Certain changes in the connective-tissue polysaccharides, such as those leading to loss of viscosity in the synovial fluid (Ropes *et al.*, 1947; Ragan and Meyer, 1949) and to abnormal metachromatic staining of the connective tissues (Altshuler and Angevine, 1949), may also be part of this reaction.

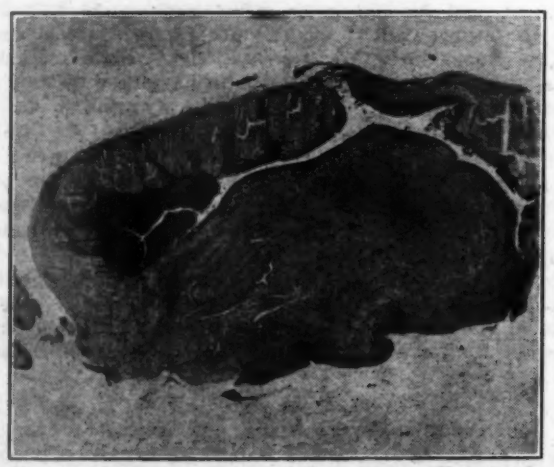


FIG. 4.—Transverse section of rheumatoid tendon lesion (stained H. and E.) (×10), illustrating relation of fibrinoid change (dark areas) to inflammatory and proliferative reaction.

The local inflammatory reaction and its relation to the fibrinoid change is well seen in the tendon lesions which are such a feature of rheumatoid disease (Kellgren and Ball, 1950). A typical example is shown in Fig. 4, which is a transverse section through part of one of the long flexor tendons of a finger. A few of the original tendon bundles have undergone fibrinoid change; adjacent to these is a mass of inflammatory granulation tissue which is also undergoing fibrinoid change in some parts. In the synovial cavities the inflammation is more widespread and its relation to fibrinoid lesions is less obvious, but they can usually be found if looked for systematically. It has generally been assumed that the fibrinoid and other connective-tissue changes result from the inflammatory reaction, but a case can be made for the opposite view.

The idea that many features of the inflammatory reaction are produced by substances liberated from damaged tissue is not new and was studied extensively by Sir Thomas Lewis (1927, 1942). More recently Moon and Tershakovec (1951) have reached the same conclusion from experiments on animals. Furthermore, Menkin (1947) has shown that inflammatory exudates contain substances which reproduce both the local and the systemic features of the inflammatory reaction, and that these substances are mostly simple peptides. If the initial lesion of rheumatoid disease is a disruption of the collagen-polysaccharide complex, together with a disintegration of the collagen molecule, a considerable number of peptides are likely to be liberated, since the collagen macro-molecule is built out of peptide chains, and it is quite possible that one or more of these peptides may have toxic properties similar to those of Menkin's peptide fractions from inflammatory exudate. Thus the inflammatory and toxic features of rheumatoid arthritis could conceivably result from a primary disintegration of collagen. Admittedly there is no direct evidence in support of this view at the moment, but it is clearly a possibility which requires investigating.

Anaemia is a very frequent finding in rheumatoid disease. It is usually of the toxic suppressive type of only moderate severity and accompanied by leucopenia. This anaemia clears up with remission of the rheumatoid process, or during suppression of its toxic and inflammatory features by cortisone or A.C.T.H. therapy, but is otherwise resistant to treatment. In some cases there may also be an iron-deficiency anaemia which will respond only to very large doses of iron given preferably by the intravenous route (Sinclair and Duthie, 1950). Much more than the calculated iron deficit must be administered, since iron utilization is interfered with as in other diseases accompanied by long-standing inflammatory changes (Slack and Wilkinson, 1949). Thus both forms of anaemia would appear to be part of the toxaemia and the inflammatory reaction.

Personality changes are a common feature of rheumatoid disease. They are usually found in patients with severe and widespread disease, and may be one of the presenting symptoms of this condition. Although they are most commonly found in patients who were previously unstable, this is not invariably the case, and an apparently normal individual may become depressed, irritable, and emotionally unstable, tending to weep at the slightest provocation. At this stage there is often marked loss of appetite and a weight loss of a stone (6.4 kg.) or more, and the sedimentation rate is considerably raised; joint symptoms, however, may be quite trivial. With the progress of the disease these personality changes often recover, in spite of increasing crippling, but they usually recur with the onset of each exacerbation of the rheumatoid process. The fact that these personality changes may be a presenting symptom excludes

the possibility of their being the result of chronic crippling disease in these cases, and it seems more likely that they are analogous to the toxic personality changes which accompany diseases such as hepatitis and influenza. Certainly the administration of cortisone and A.C.T.H. appears to have a most striking and immediate effect on these changes, even in those cases in which the crippling joint disease remains largely unaffected.

Disorders of the peripheral circulation are common in rheumatoid disease and may be one of its presenting features. We have made a special study of this aspect of rheumatoid disease (Janus, 1952), and it appears that this disturbance is complex, consisting in a decrease of cutaneous blood flow, particularly in the extremities, together with an increase of deep blood flow in the limbs, especially in severely affected joints. There is also an increased cardiac output as judged by ballistocardiographic observations. The cutaneous flow may be increased by sympathectomy and the disturbance of cutaneous and deep flow, and cardiac output may be corrected by the administration of cortisone or A.C.T.H. Although the exact mechanism of these disturbances has not been fully worked out, their relief by cortisone and A.C.T.H. suggests that a chemical disorder is involved at some stage.

There are other clinical features of rheumatoid disease which might be discussed, such as changes in skeletal muscle, visceral, ocular, and cutaneous manifestations, the occasional occurrence of amyloid disease, and so on; but these must be left to another occasion, since we still have the role of the adrenal cortex to consider.

The Adrenal Cortex

When Hench *et al.* (1949) first demonstrated the remarkable effects of cortisone upon many of the features of rheumatoid disease it seemed as if the adrenal cortex must play some central part in the pathogenesis of this disease. But it very soon became apparent that the clinical features of many other diseases could be strikingly modified by giving cortisone or A.C.T.H. Furthermore, patients with demonstrable disorders of the adrenal cortex do not suffer specially from rheumatoid disease. The role of the cortical hormones is therefore best considered in the light of their general homoeostatic functions, which have been recently reviewed by Sayers (1950).

The results of many experiments on animals, together with the experience gained from the administration of cortisone and A.C.T.H. to patients suffering from all kinds of diseases, have led to the following conclusion. The pituitary adrenocortical system responds rapidly to any stress by the production of relatively large amounts of steroids similar to or identical with compound F and cortisone. The effects of large amounts of these steroids produced endogenously or administered from without are manifold, but they concern chiefly the body's reactions to insults of various kinds. Thus these steroids interfere with wound-healing (Ragan, Grokoest, and Boots, 1949; Ragan, Howes, *et al.*, 1949; Baker and Whitaker, 1950; Bangham, 1951), with the repair of fractures (Blunt *et al.*, 1950), and with the local inflammatory response to trauma and chemical irritants (Jones and Meyer, 1950; Michael and Whorton, 1951; Shapiro *et al.*, 1951). They reduce both the local and the systemic inflammatory reactions to infection with bacteria or virus (Kass *et al.*, 1950; Kass and Finland, 1951), and this may have deleterious effects, particularly in tuberculosis (Hart and Rees, 1950). They also suppress the clinical features of allergic disease (Randolph and Rollins, 1950; Carey *et al.*, 1950) and interfere with the tuberculin reaction (Long and Miles, 1950) and the Arthus phenomenon (Germuth and Ottinger, 1950), and they modify the reaction to tissue homografts (Billingham, Krohn, and Medawar, 1951).

Whether the cortical steroids prevent damaged tissues from liberating the substances normally responsible for the inflammatory and allergic reactions and the processes of healing, or whether they neutralize or destroy these substances, or protect intact tissues against their action, is as yet uncertain; but it has been established that their main action is a local one in the tissues themselves.

Cortisone and A.C.T.H.

In rheumatoid disease the administration of cortisone and A.C.T.H. produces a striking and prompt relief of symptoms in most cases. Thus spontaneous pain is usually relieved, and joint tenderness is markedly reduced, and this results in a striking improvement of function in the limbs. Local warmth and swelling are also reduced, and the reduction in swelling may be rapid and complete when the swelling is due to an excess of fluid in the joints and other structures. Fever and the other constitutional features of the toxaemia and inflammatory reaction may also be controlled, but the diseased connective tissues do not appear to return to a fully normal condition (Hench *et al.*, 1950) and cellular changes may persist, although symptoms such as pain have been adequately suppressed (Johnson, 1950).

Where the active disease process is of slight severity and limited extent patients can be kept symptom-free or almost so for months or even years by continuous hormone therapy (Boland and Headley, 1950; Ward *et al.*, 1951); but, where the active disease process is severe and widespread, satisfactory relief can often be obtained only by employing a dosage high enough to produce definite signs of hypercorticism. In this context it must be remembered that severe anatomical changes in the joints and other tissues may be found in patients in whom the disease process has become largely inactive. Furthermore, we have found that the degree of response to cortisone and A.C.T.H. varies greatly from one patient to another quite apart from the extent of their disease.

Although the administration of cortisone or A.C.T.H. in high enough dosage seems to suppress most of the symptoms of rheumatoid disease in the majority of patients, only a small proportion of these patients can obtain a really worth-while relief with a hormonal dosage which can be safely continued for long periods, and the effect of such suppressive therapy upon the long-term evolution of the rheumatoid disease process remains to be evaluated.

There are, however, some features of rheumatoid disease which appear to be less readily altered by the administration of cortisone or A.C.T.H. Thus in rheumatoid nodules removed from patients who have had intensive courses of these hormones we have seen the usual fibrinoid core which differs little from that seen in similar nodules before treatment. On the other hand, the surrounding zones of inflammatory and proliferative reaction were much less evident during hormone therapy. Similar findings have been reported by Hunt and Blanchard (1951) and Fienberg and Colpoys (1951), though they claim that the fibrinoid itself was reduced during prolonged and intensive hormone therapy and that it became more evident again after hormone withdrawal.

We have not seen any recovery of generalized connective-tissue atrophy during hormone therapy, and no reports of such recovery are available. Indeed, it would be surprising if such a recovery were to take place, since connective-tissue atrophy is one of the features of hypercorticism (Albright and Reifenstein, 1948).

The agglutination reaction shows no consistent change during cortisone or A.C.T.H. therapy according to Ragan, Grokoest, and Boots (1949), and Svartz and Schlossmann (1950), and our own findings are in agreement with this.

Thus there are features of rheumatoid disease which do not appear to be readily relieved by the adrenocortical hormones, and these features may well be closely related to the essential rheumatoid process, which apparently remains unaffected by hormone therapy. The dramatic change in the clinical picture which can often be produced by the administration of cortisone or A.C.T.H. in patients

with rheumatoid disease may very well be due to the suppression of the body's reaction to the essential rheumatoid lesion, the clinical picture in a given patient at any one time being the product of the connective-tissue disease, the body's reaction to this, and the suppressing activity of the pituitary-adrenal system or administered cortisone and A.C.T.H. Since each of these may vary independently it is not surprising that the clinical course of rheumatoid disease is so variable and so full of pleasant and also unpleasant surprises.

Other Factors

It is generally agreed that salicylates have a profound effect upon the inflammatory features of rheumatic fever. In rheumatoid disease they seem to have a much smaller but definite effect, and for some obscure reason aspirin appears to be more effective than sodium salicylate. If the dosage is pushed to the limits of tolerance some relief of pain and swelling is obtained in most cases, and in a few the relief is marked and comparable to that obtained in rheumatic fever. In these responsive cases relief of pain and swelling is accompanied by an increase of cutaneous blood flow and a rising eosinophil count (Janus, 1950). These findings suggest that aspirin has more than an analgesic action, and the rising eosinophil count makes it most unlikely that the relief of symptoms is due to adrenocortical stimulation.

From clinical observations it is clear that trauma and excessive wear and tear have a very adverse effect upon the disease process, and may even precipitate a local or general exacerbation. Indeed, the localized rheumatoid disease which may follow trauma in susceptible subjects causes frequent disputes over matters of compensation. Conversely, rest is beneficial. Where disease activity is localized, local rest may be obtained with appropriate plaster splintage, but where the disease is generalized rest in bed is essential. It is not yet clear whether rest acts upon the connective-tissue lesion or upon the inflammatory reaction, but its good effects are commonly long-lasting, which suggests that it may influence the course of the essential rheumatoid process. Rest has a favourable effect only upon the active disease process; when this has settled down and the patient is left with stiff joints and wasted muscles, active exercise, physiotherapy, and the whole rehabilitation programme which can be provided so well at our spas are all invaluable aids in regaining function and preparing the patient for a return to active life.

In the three controlled trials of gold therapy which have been carried out to date (Ellman *et al.*, 1940; Fraser, 1945; Adams and Cecil, 1950) the cases receiving gold showed a greater degree of improvement than the control group, and this has been our own experience. Thus gold salts may well have some influence upon the rheumatoid disease process, but their mode of action remains obscure.

The search for aetiological factors continues, and has so far been unsuccessful, but with a clearer understanding of the essential lesion of rheumatoid disease this search may possibly be directed into more fruitful channels.

Summary and Conclusions

The views expressed in these lectures may be summarized in the following concepts:

(1) The rheumatic diseases are essentially diseases of the supporting system of the body. This system is made up of connective tissues in varying degrees of organization, and it is mainly through a closer study of these tissues and the processes which maintain them that we shall come to understand and control this group of diseases.

(2) The intercellular collagen-polysaccharide complex is the functionally essential part of the connective tissues, and it is tentatively suggested that a disorder of this complex may be the primary lesion in both rheumatoid arthritis and degenerative joint disease.

(3) In rheumatoid disease there may be a loosening of the collagen-polysaccharide complex which allows the collagen molecule to disintegrate into relatively simple peptides which diffuse out of the affected tissue. When relatively large portions of tissue are affected a residual material rich in polysaccharide, and probably a glycoprotein, replaces the damaged tissue, thus producing the fibrinoid lesions. Some of the disintegration products of collagen may have toxic properties, and it is possible that these may account for some if not all of the manifold toxic and inflammatory features of rheumatoid disease.

(4) In degenerative joint disease the primary lesion appears to be a loss of chondroitin sulphate from the articular cartilage. This leaves the collagen fibrils unsupported, so that they may become changed and broken up with wear and tear. No toxic substances appear to be liberated during this process, and the clinical features of the disease are mainly due to mechanical disorganization of the affected joints.

These concepts are clearly gross over-simplifications and will probably have to be modified or even changed altogether as new data become available, since at this moment many brilliant workers are attacking these problems with a variety of new technical weapons. Nevertheless some synthesis of all the work done must be attempted from time to time if only to provide us with some definite point of view from which we may be able to see new and possibly more fruitful lines of investigation.

References

Abramson, D. J., and Kamberg, S. (1949). *J. Bone Jt Surg.*, 31A, 275.
Adams, C. H., and Cecil, R. L. (1950). *Ann. intern. Med.*, 33, 163.
Albright, F., and Reifenstein, E. C. (1948). *Parathyroid Glands and Metabolic Bone Disease*, p. 165. Williams and Wilkins Co., Baltimore.
Alshuler, C. H., and Angevine, D. M. (1949). *Amer. J. Path.*, 25, 1061.
Askanazy, M. (1921). *Virchows Arch.*, 234, 111.
Astbury, W. T. (1940). *J. int. Soc. Leath. Chem.*, 24, 69.
—— (1947). *Proc. roy. Soc. B*, 134, 303.
Baker, B. L., and Whitaker, W. L. (1950). *Endocrinology*, 46, 544.
Ball, J. (1950). *Lancet*, 2, 520.
—— (1952). In press.
Bangham, A. D. (1951). *Brit. J. exp. Path.*, 32, 77.
Bauer, W., and Bennett, G. A. (1936). *J. Bone Jt Surg.*, 18, 1.
Bear, R. S. (1942). *J. Amer. chem. Soc.*, 64, 727.
Billingham, R. E., Krohn, P. L., and Medawar, P. B. (1951). *British Medical Journal*, 1, 1157; 2, 1049.
Blunt, J. W., Plotz, C. M., Lattes, R., Howes, E. L., Meyer, K., and Ragan, C. (1950). *Proc. Soc. exp. Biol., N.Y.*, 73, 678.
Boland, E. W., and Headley, N. E. (1950). *J. Amer. med. Ass.*, 144, 365.
Bowes, J. H., and Kenten, R. H. (1948). *Biochem. J.*, 43, 358.
Bresler, S. E., Finogenov, P. A., and Ya Frenkel, S. (1950). *Doklady Akad. Nauk, S.S.S.R.*, 72, 555.
Buzagh, A. von (1942). *Kolloid Z.*, 101, 149.
Bywaters, E. G. L. (1937). *J. Path. Bact.*, 44, 247.
Carey, R. A., Harvey, A. M., Howard, J. E., and Wagley, P. F. (1950). *Bull. Johns Hopk. Hosp.*, 87, 354, 387.
Chain, E., and Duthie, E. S. (1940). *Brit. J. exp. Path.*, 21, 324.
Consden, R., Glynn, L. E., and Stanier, W. M. (1952). *Biochem. J.*, 50, xix.
Duran-Reynals, F. (1942). *Bact. Rev.*, 6, 197.
Ellman, P., Lawrence, J. S., and Thorold, G. P. (1940). *British Medical Journal*, 2, 314.
Fagge, C. H. (1877). *Trans. path. Soc. Lond.*, 28, 201.
Fienberg, R., and Colpoys, F. L. (1951). *Amer. J. Path.*, 27, 925.
Fraser, T. N. (1945). *Ann. rheum. Dis.*, 4, 71.
Garrod, A. E., Allbutt, T. C., and Rolleston, H. D. (1907). *System of Medicine*, vol. 3. Macmillan, London.
Germuth, F. G., and Ottinger, B. (1950). *Proc. Soc. exp., Biol., N.Y.*, 74, 815.
Gersh, I., and Catchpole, H. R. (1949). *Amer. J. Anat.*, 85, 457.
Goldthwait, J. E. (1904). *Boston med. surg. J.*, 151, 529.
Hale, C. W., (1946). *Nature, Lond.*, 157, 802.
Hart, P. D'A., and Rees, R. J. W. (1950). *Lancet*, 2, 391.
Heberden, W. (1802). *Commentaries on the History and Cure of Disease*. T. Payne, London.
Heine, J. (1926). *Virchows Arch.*, 260, 521.
Heller, G., Jacobson, A. S., and Kolodny, M. H. (1949). *Proc. Soc. exp. Biol., N.Y.*, 72, 316.
Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, 24, 181.
—— —— —— —— (1950). *Arch. intern. Med.*, 85, 545.
Hirsch, C. (1944). *Acta chir. scand.*, 90, Suppl. 83.
Hunt, T. E., and Blanchard, A. J. (1951). *Ann. Rheum. Dis.*, 10, 337.
Janus, O. (1950). *British Medical Journal*, 2, 1244.
—— (1952). In preparation.
Jawetz, E., and Hook, E. V. (1950). *Proc. Soc. exp. Biol., N.Y.*, 70, 650.
Johnson, R. W. (1950). *J. Bone Jt Surg.*, 32A, 475.
Jones, I. S., and Meyer, K. (1950). *Proc. Soc. exp. Biol., N.Y.*, 74, 102.
Kass, E. H., and Finland, M. (1951). *New. Engl. J. Med.*, 244, 464.
—— Ingbar, S. H., and Finland, M. (1950). *Ann. intern. Med.*, 33, 1081.

Kellgren, J. H., and Ball, J. (1950). *Ann. rheum. Dis.*, **9**, 48.
—— —— Astbury, W. T., Reed, R., and Beighton, E. (1951). *Nature, Lond.*, **168**, 493.
—— and Moore, R. (1952). *British Medical Journal*, **1**, 181.
Klemperer, P. (1950). *Amer. J. Path.*, **26**, 505.
Klinge, F. (1933). *Ergebn. Path.*, **27**, 1.
—— (1934). *Handb. spez. path. Anat. Hist.*, edited by O. Lubarsch, and F. Henke, vol. 9/2, p. 107. Springer, Berlin.
Lewis, T. (1927). *Blood Vessels of the Human Skin and their Responses* London.
—— (1942). *Pain*. MacMillan Co., New York.
Lison, L. (1935). *C.R. Soc. Biol., Paris*, **118**, 821.
Long, D. A., and Miles, A. A. (1950). *Lancet*, **1**, 492.
McManus, J. F. A. (1946). *Nature, Lond.*, **158**, 202.
Mau, C. (1929). *Z. orthop. Chir.*, **51**, 106.
Menkin, V. (1947). *Lancet*, **1**, 660.
Meyer, K. (1947). *Physiol. Rev.*, **27**, 335.
—— (1950). *Connective Tissues*, p. 88. Trans. 1st Conf. Josiah Macey Foundation, New York.
Michael, M., and Whorton, C. M. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 754.
Moon, V. H., and Tershakovec, G. A. (1951). *Arch. Path.*, **52**, 369.
Nageotte, J. (1927). *C.R. Acad. Sci.*, **184**, 115.
Neuberger, A., Perrone, J. C., and Slack, H. G. B. (1951). *Biochem. J.*, **49**, 199.
Neuman, R. E., and Logan, M. A. (1950). *J. biol. Chem.*, **184**, 299.
Neumann, E. (1880). *Arch. mikr. Anat.*, **25**, 130.
Paronen, I. (1948). *Acta med. scand.*, Suppl. 212.
Partridge, S. M. (1943). *Biochem. J.*, **43**, 387.
Penney, E. J. R., and Balfour, B. M. (1949). *J. Path. Bact.*, **61**, 171.
Perrone, J. C., and Slack, H. G. B. (1951). *Biochem. J.*, **49**, lxxii.
Porter, K. R., and Vanamee, P. (1949). *Proc. Soc. exp. Biol., N.Y.*, **71**, 513.
Ragan, C., Grokoest, A. W., and Boots, R. H. (1949). *Amer. J. Med.*, **7**, 741.
—— Howes, E. L., Plotz, C. M., Meyer, K., and Blunt, J. W. (1949). *Proc. Soc. exp., Biol., N.Y.*, **72**, 718.
—— and Meyer, K. (1949). *J. clin. Invest.*, **28**, 56.
Randolph, T. G., and Rollins, J. P. (1950). *J. Allergy*, **21**, 260.
Rich, A. R., and Gregory, J. E. (1943). *Bull. Johns Hopk. Hosp.*, **72**, 65.
Ropes, M. W., Robertson, W. B., Rossmeisl, E. C., Peabody, R. B., and Bauer, W. (1947). *Acta med. scand.*, Suppl. 196.
Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Proc. Soc. exp. Biol., N.Y.*, **68**, 1.
Sayers, G. (1950). *Physiol. Rev.*, **30**, 241.
Scaglietti, O., and Casuccio, C. (1936). *Chir. Organi Mov.*, **20**, 469.
Schmitt, F. O., Hall, C. E., and Jakus, M. A. (1942). *J. cell. comp. Physiol.*, **20**, 11.
Selye, H. (1950). *Stress*. Acta Inc., Montreal.
Shapiro, R., Taylor, B., and Taubenhaus, M. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 854.
Sinclair, R. J. C., and Duthie, J. J. R. (1950). *British Medical Journal*, **2**, 1257.
Slack, H. G. B., and Wilkinson, J. F. (1949). *Lancet*, **1**, 11.
Sulkin, S. E., Pike, R. M., and Coggeshall, H. C. (1949). *Proc. Soc. exp. Biol., N.Y.*, **70**, 475.
Svartz, N., and Schlossmann, K. (1950). *Ann. rheum. Dis.*, **9**, 377.
Sydenham, T. (1676). *Works of Thomas Sydenham, M.D.* Translated from Latin edition by Greenhill, 1848. London.
Sylvén, B. (1941). *Acta chir. scand.*, Suppl. 66.
—— Paulson, S., Hirsch, C., and Snelman, O. (1951). *J. Bone Jt Surg.*, **33A**, 333.
Ward, L. E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S. (1951). *Proc. Mayo Clin.*, **26**, 361.
Wolbach, S. B. (1933). *Amer. J. Path.*, **9**, 689.
Wu, T. T. (1937). *Virchows Arch.*, **300**, 373.

Meeting in Geneva on May 19 to discuss birth control, the World Health Organization decided not to follow further the proposal put forward by the Norwegian delegate to study the "health aspects" of the world population problem (*New York Times*, May 20). This was because delegates from several predominantly Roman Catholic countries had said that action in this field would endanger the whole existence of W.H.O. Dr. Karl Evang had suggested they should look into the possibility of government propagation of birth-control methods in over-populated countries. The Belgian delegate put forward a counter-proposal forbidding any action of this sort. Had this been accepted it would have put a stop to the work already being done by W.H.O. in India and various other countries on family planning. The question was debated for two days, and then all the delegates agreed to drop the whole matter without a vote, in the interests of harmony. Secretariat officials said afterwards that they did not consider themselves bound in any way to stop advising governments on family planning as a result of this discussion. Only a formal decision by the Assembly could do this. In a letter to *The Times* on May 23, Lord Horder, commenting on the Roman Catholic threat of a mass walk-out in the event of acceptance of Norway's proposals, says that by their action they have possibly "prevented action which might have saved millions of lives." The problem of population, he writes, increases with every hour of every day and, without the knowledge of birth control, can be solved only by disease and other means involving much human suffering.

THE PREVENTION OF STREPTOMYCIN RESISTANCE BY COMBINED CHEMOTHERAPY

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The value of chemotherapy, combining streptomycin and P.A.S., in the treatment of certain forms of pulmonary tuberculosis was demonstrated in a Medical Research Council (1950) report of a controlled investigation. In particular it was shown that association of P.A.S. with streptomycin substantially reduced the risk of development of drug resistance. The daily dose of P.A.S. used was 20 g. of the sodium salt, a dose which produced gastro-intestinal discomfort in more than half the patients. It was decided to investigate whether smaller doses of P.A.S. would have the same effect on drug resistance: that investigation has been completed, and the results are reported here. The inquiry was planned and directed, as the previous trial, by a joint subcommittee of the Medical Research Council's Streptomycin in Tuberculosis Trials Committee and the British Tuberculosis Association's Research Committee, and the centres at which the work was carried out were the same as before.*

It was decided to have three concurrent groups, with the same type of disease as in the previous trial, and to use the same daily dose of streptomycin for all groups, but different doses of P.A.S. (5, 10, or 20 g.). The main analysis would concentrate on the results of streptomycin sensitivity tests. Since these would give a clear numerical differentiation, smaller groups were needed than for the previous trial, and the collection of cases, which had started in November, 1949, was stopped at the end of December, 1950, with 115 patients in the investigation.

*Members of the Joint Subcommittee: Sir Geoffrey Marshall (chairman), Professor R. Cruickshank, Dr. Marc Daniels, Professor F. R. G. Heaf, Professor A. Bradford Hill, Dr. J. V. Hurford, Dr. K. Perry, Dr. J. G. Scadding, Dr. W. E. Snell, and Dr. P. D'Arcy Hart (secretary).

Centres, clinicians, and pathologists collaborating:

Brompton Hospital, London.—Clinician: Dr. J. R. Bignall (working under the direction of the honorary staff of Brompton Hospital). Pathologists: Dr. J. W. Clegg, Dr. T. D. M. Martin.

Clare Hall County Hospital, Herts.—Clinician: Dr. T. A. W. Edwards. Pathologists: Dr. H. Loewenthal, Dr. R. F. Welch.

Colindale Hospital, London.—Clinicians: Dr. W. E. Snell, Dr. G. O'Malley, Dr. W. C. Harris. Pathologists: Dr. J. L. Hamilton-Paterson, Dr. E. D. Hoare.

Aintree Hospital (late Fazakerley Sanatorium), Liverpool.—Clinicians: Dr. O. F. Thomas, Dr. J. Hamilton Gifford. Pathologists: Professor A. W. Downie, Dr. C. A. St. Hill.

Harefield County Hospital, Middlesex.—Clinicians: Dr. L. E. Houghton, Dr. G. P. Maher-Loughnan, Dr. J. Sumner. Pathologist: Dr. E. Nassau.

King George V Sanatorium, Surrey.—Clinicians: Dr. J. V. Hurford, Dr. M. Francis. Pathologist: Dr. N. P. L. Wildy.

London Chest Hospital, London.—Clinician: Dr. L. J. Grant. Pathologist: Dr. W. I. Leslie.

London Hospital Annexe, Essex.—Clinicians: Dr. K. Perry, Dr. N. Lloyd Rusby, Dr. D. C. L. Beatty. Pathologist: Dr. F. C. O. Valentine.

Sully Hospital, Glamorgan.—Clinician: Dr. L. R. West. Pathologist: Dr. Ruth L. Milne.

Yardley Green Hospital, Birmingham.—Clinician: Dr. Hector J. T. Ross. Pathologist: Dr. B. R. Sandiford.

Dr. Marc Daniels, of the M.R.C. Tuberculosis Research Unit, was responsible for the co-ordination of the trial, and he also analysed the results and prepared the report for the Committee. Professor A. Bradford Hill was responsible for the statistical design of the trial. The radiological results were assessed by Dr. G. Simon.

Plan and Conduct of the Trial

The methods employed were similar to those of the previous combined chemotherapy trial and of the initial streptomycin trial. The type of case to be investigated was defined as follows: acute progressive bilateral pulmonary tuberculosis, believed to be of recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15–30. Letters were sent, through the regional hospital boards, to chest physicians and medical superintendents of general hospitals in the areas from which the chosen centres could receive patients; the letters outlined the proposed scheme and asked that particulars and *x*-ray films of possibly suitable patients should be sent to the Tuberculosis Research Unit. Particulars and films of cases submitted were considered by the Committee's selection panel, who decided if a case came within the limits of the definition. When a patient had been accepted as suitable, arrangements were made through the regional hospital board for admission to one of the centres; these patients were given high priority.

After acceptance by the panel the determination of the treatment group in each case was made by reference to a list (based upon random sampling numbers) held confidentially in the Tuberculosis Research Unit. After admission each patient was kept under observation for at least one week before treatment for the trial started; during that week all prescribed preliminary examinations were carried out. Clinical observations were entered on standard record forms designed particularly for this trial. When six months' observation had been completed in the required number of cases, all records and *x*-ray films were sent to the Tuberculosis Research Unit for analysis. The analysis presented here is therefore based on all available material from the centres at which the patients were treated, but has been made independently of those centres. Changes in *x*-ray appearance were assessed without the assessor having any knowledge of the treatment given.

Number of Patients in the Trial

The records of 115 patients were available for the analysis of results; for 42 of them the daily dose of sodium P.A.S. was 20 g. (group SP 20), for 39 it was 10 g. (SP 10), and for 34 it was 5 g. (SP 5).

A total of 133 cases had been accepted by the panel (46 SP 20, 46 SP 10, 41 SP 5), but for various reasons 18 were omitted from the study. Thus four cases were excluded after acceptance because they were never confirmed bacteriologically and therefore failed to meet the criteria of admission. Eight were excluded because it was found after acceptance that they had already been treated with streptomycin or P.A.S., or both; this would have affected the results of sensitivity tests. One patient refused treatment, and another took his own discharge after six weeks' treatment. Two died before treatment could be started. In two cases the physician under whose care the patient was admitted decided that collapse therapy was necessary immediately in addition to the chemotherapy prescribed for the trial.

Condition on Admission

In Table I is shown, for the three treatment groups, the condition of the patients before treatment started, as reflected by their general condition (assessment by the clinician in charge), temperature (Fahrenheit, by mouth), sedimentation rate (Westergren, 200 mm. reading at one hour), and extent of cavitation as assessed on one single film, without tomograms.

As in the previous trials, the data indicate that clinically most of the patients were fairly ill, and in about half of them radiography revealed gross cavitation (2-plus or 3-plus). The distribution was similar in the three groups; there were rather more severely ill patients in the SP 10 group, but the differences are not statistically significant.

TABLE I.—*Condition of Patients on Admission*

	SP 20*		SP 10†		SP 5‡	
	No.	%	No.	%	No.	%
Total	42	*100*	39	*100*	34	*100*
General condition:						
Good	2	*5*	3	*8*	1	*3*
Fair	23	*55*	17	*44*	21	*62*
Poor	17	*40*	19	*49*	12	*35*
Average evening temp. in first week:§						
Afebrile‖	5	*12*	6	*15*	8	*24*
Less than 99° F. (37·2° C.), but febrile	14	*33*	9	*23*	7	*21*
99–99·9° F. (37·2–37·75° C.)	16	*38*	14	*36*	15	*44*
100° F. + (37·8° C.+)	7	*17*	10	*26*	4	*12*
Sedimentation rate:						
0–10	0	*0*	0	*0*	2	*6*
11–20	2	*5*	4	*10*	2	*6*
21–50	20	*48*	17	*44*	13	*38*
51+	20	*48*	18	*46*	17	*50*
Cavitation:						
Nil	3	*7*	5	*13*	8	*24*
1-plus	19	*45*	10	*26*	9	*26*
2-plus	16	*38*	22	*56*	11	*32*
3-plus	4	*10*	2	*5*	6	*18*

* SP 20. Group treated with 1 g. streptomycin and 20 g. P.A.S. (sodium salt) daily.
† SP 10. Group treated with 1 g. streptomycin and 10 g. P.A.S. (sodium salt) daily.
‡ SP 5. Group treated with 1 g. streptomycin and 5 g. P.A.S. (sodium salt) daily.
§ Temperature taken by mouth.
‖ A patient was considered afebrile if *all* temperatures recorded were below 99° F.

Treatment

A. First Three Months

All patients were treated by rest in bed, and all had streptomycin, 1 g. daily, by intramuscular injection at 8 a.m. In addition, sodium P.A.S. was given in daily doses of 20 g., 10 g., and 5 g. for the SP 20, SP 10, and SP 5 groups respectively; it was given by mouth, in four divided doses, at 8 a.m., noon, 4 p.m., and 8 p.m.

Treatment in each case started at the end of a preliminary observation week, and continued for three months. It was recommended that during these three months no treatment should be given other than rest in bed and the prescribed chemotherapy, unless the condition so changed that other measures became urgent and desirable. In fact, artificial pneumoperitoneum was induced in the second month of treatment in two cases, both in the SP 10 group.

B. Second Three Months

In the protocols of the trial it was suggested that during the second three-months period any other treatment considered appropriate might be initiated by the clinician in charge of the patient; it was strongly recommended that any further chemotherapy combining the two drugs should not be different from that given in the first three months.

Additional Chemotherapy.—Chemotherapy was continued during this period in 14 cases: seven in the SP 20 group, three in the SP 10, and four in the SP 5. Further details of these cases are given in the study of sensitivity results.

Collapse Therapy.—Collapse therapy was applied in 36 cases (Table II). In 22 cases it was induced in the fourth month, shortly after the end of the prescribed chemotherapy course.

TABLE II.—*Collapse Therapy*

	SP 20	SP 10	SP 5
Artificial pneumothorax maintained	3	1	3
" " abandoned	0	2	2
" pneumoperitoneum	11	9	5
	14 (33%)	12 (31%)	10 (29%)

Toxicity

No severe vestibular disturbance was noted. Giddiness was recorded in 8 of the 115 cases (7%)—five in the first month and three in the second. One of the cases occurred

in the SP 5 group, three in the SP 10, and four in the SP 20.

Apart from rashes accompanying febrile toxic reactions described below, and apart from some dryness and scaliness of the skin noted in many cases, a rash was observed in seven cases—three on the smallest dose of P.A.S. and four on the highest dose. Treatment was not stopped and the rash subsided, in four cases after administration of antihistamines, though whether the latter was responsible for the improvement is not clear.

Gastro-intestinal symptoms were infrequent and mild in the two groups on smaller doses of P.A.S.: four (12%) of the SP 5 group and six (15%) of the SP 10 had loose stools in the first or second month. In the group receiving 20 g. of P.A.S. the incidence was much greater; gastro-intestinal symptoms were recorded in 22 cases (52%): in five there was diarrhoea persisting on and off throughout treatment, in nine loose stools, in seven nausea, and in six vomiting. However, in only one of these cases was the disturbance severe enough to demand reduction of the dose; the daily dose was reduced to 10 g. in the third month.

In five cases there were in the third or fourth week of treatment febrile toxic reactions which necessitated temporary cessation of treatment. In one case in the SP 20 group the reaction was attributable to P.A.S.: on the 23rd day a papular rash developed and the temperature rose, the reaction subsiding when P.A.S. was stopped; P.A.S. treatment was started again with 2.5 g. daily, and it was possible to lead up slowly again to the full dose of 20 g. without mishap. In one case (SP 10 group) the streptomycin was definitely responsible: the temperature rose again each time a streptomycin injection was given; finally, dihydrostreptomycin was substituted and was well tolerated. In three cases (one SP 5 and two SP 10) the toxic reaction was attributable to both drugs; desensitization was undertaken to streptomycin and then to P.A.S., and both drugs were then well tolerated.

Clinical Results

The trial was designed especially to answer questions concerning streptomycin sensitivity. It was expected from the outset that in clinical results there would be little difference between the three groups, since in the previous trial the difference between the group receiving streptomycin only and the one receiving streptomycin plus 20 g. of P.A.S. had been small. Accordingly the clinical analysis which follows is much briefer than that for the previous trial.

Mortality.—Two patients died; both were in the group receiving 5 g. of P.A.S. daily. One of them had improved during the first three months, but got rapidly worse subsequently, and died in the sixth month; the other showed no response to chemotherapy, and died in the fifth month.

Radiological Assessment.—The changes in radiological appearance at three months and six months are shown in Table III. There was no significant difference between the three groups, either at the end of the three-months course of chemotherapy or after three more months of observation. Nearly 90% of these patients with acute progressive tuberculosis who were at first thought to be unsuitable for collapse therapy had improved at the end of six months; the improvement was considerable (2-plus or 3-plus) in half of them. The results for men and women were analysed separately and, contrary to the findings of the previous trial, the difference was here in favour of the men: 59% showed considerable improvement, compared with 45% of the women. The difference, however, is not statistically significant.

TABLE III.—*Assessment of Radiological Appearance at Three Months and Six Months Compared with Appearance on Admission*

	At 3 Months						At 6 Months					
	SP 20		SP 10		SP 5		SP 20		SP 10		SP 5	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Improvement:												
3-plus	0	*0*	0	*0*	1	*3*	4	*10*	7	*18*	4	*12*
2-plus	2	*5*	2	*5*	1	*3*	18	*44*	12	*31*	15	*44*
1-plus	22	*52*	19	*49*	22	*65*	14	*34*	15	*38*	11	*32*
No change	18	*43*	15	*38*	8	*24*	4	*10*	4	*10*	2	*6*
Deterioration	0	*0*	3	*8*	2	*6*	1	*2*	1	*3*	0	*0*
Death ..	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*	2	*6*
Total	42	*100*	39	*100*	34	*101*	41*	*100*	39	*100*	34	*100*

* One *x*-ray film missing.

General Condition.—The general condition at the end of six months was thought by the clinician in charge to have improved in all but four of the SP 5 group, all but four of the SP 10 group, and all but two of the SP 20 group. The improvement was considerable in 56%, 49%, and 52% respectively.

Temperature.—In Table IV are shown the number of patients who, febrile at the start of treatment, had become afebrile at the end of three months and six months. Here again there is no appreciable difference between the three groups. In general the results were most favourable in those with average temperature under 100° F. (37.8° C.); 56 of the 75 such patients (75%) were afebrile at the end of three months' treatment, compared with only 5 of 21 (24%) more acutely febrile cases.

TABLE IV.—*Temperature Changes in Patients Febrile on Admission*

Average Evening Temperature During Week Following Admission	Group	Total	No. of Patients Afebrile at: 3 Months		6 Months	
			No.	%	No.	%
Less than 99° F. (37·2° C.)	SP 5	7	5	*71*	5	*71*
	SP 10	9	7	*78*	8	*89*
	SP 20	14	10	*71*	11	*79*
99–99·9° F. (37·2–37·75° C.)	SP 5	15	12	*80*	11	*73*
	SP 10	14	11	*79*	8	*57*
	SP 20	16	11	*69*	11	*69*
100° F.+ (37·8° C.+) ..	SP 5	4	1	*25*	1	*25*
	SP 10	10	2	*20*	1	*10*
	SP 20	7	2	*29*	3	*43*
All febrile cases	SP 5	26	18	*69*	17	*65*
	SP 10	33	20	*61*	17	*52*
	SP 20	37	23	*62*	25	*68*

Sedimentation Rate.—The data on sedimentation rate in Table V show somewhat better results in the SP 5 group than in the other two—53% normal at six months against 41% in SP 10 and 34% in SP 20; but the difference is not significant. The total number of patients with an E.S.R. within normal limits was two before treatment started, 32 (28%) at the end of three months, and 48 (42%) at six months.

TABLE V.—*Changes in Sedimentation Rate (Westergren)*

	Group	Total	Sedimentation Rate 0–10	11–20	21–50	51+	Deaths
At start of treatment	SP 5	34	2	2	13	17	—
	SP 10	39	—	4	17	18	—
	SP 20	42	—	2	20	20	—
At 3 months ..	SP 5	34	11	9	8	6	—
	SP 10	39	14	6	15	4	—
	SP 20	42	7	17	11	7	—
,, 6	SP 5	43	18	5	6	3	2
	SP 10	39	16	4	15	4	—
	SP 20	41*	14	10	12	5	—

* No result available for one patient.

Bacterial Content of Sputum

Sputum was examined on entry and twice a month by smear and culture; if there was no sputum, or the smear examination was negative, material was cultured from a laryngeal swab or gastric lavage. No case was to be declared

bacteriologically negative unless these examinations had been done. The results of these examinations are set out in Tables VI and VII.

TABLE VI.—*Presence of Tubercle Bacilli*

Time	Group	Total Patients from Whom Specimens were Examined	Total Specimens Examined		Positive Direct Examination		Negative Direct Examination Positive Culture		Negative Direct Examination and Culture	
			No.	%	No.	%	No.	%	No.	%
On admission	SP 5	34	34	100	26	77	8	23	0	0
	SP 10	39	39	100	35	90	4	10	0	0
	SP 20	42	42	100	33	79	9	21	0	0
1st month	SP 5	34	74	100	37	50	29	39	8	11
	SP 10	38	79	100	56	71	13	16	10	13
	SP 20	40	87	100	59	68	16	18	12	14
2nd month	SP 5	34	79	100	26	33	30	38	23	29
	SP 10	37	85	100	42	49	28	33	15	18
	SP 20	40	94	100	51	54	26	28	17	18
3rd month	SP 5	30	70	100	19	27	19	27	32	46
	SP 10	38	84	101	30	36	25	30	29	35
	SP 20	41	98	100	29	30	24	24	45	46
4th month	SP 5	33	73	100	17	23	16	22	40	55
	SP 10	38	82	101	16	20	27	33	39	48
	SP 20	40	86	100	23	27	14	16	49	57
5th month	SP 5	32	70	100	26	37	20	29	24	34
	SP 10	39	79	100	35	44	14	18	30	38
	SP 20	37	84	100	26	31	24	29	34	40
6th month	SP 5	32	71	100	24	34	14	20	33	46
	SP 10	36	70	100	34	49	14	20	22	31
	SP 20	38	81	101	33	41	20	25	28	35

TABLE VII.—*Number of Patients with Negative Results (Direct Examination and Culture) Throughout Successive Months*

Month After Treatment Started	Group	Total Patients from Whom Specimens were Examined (A)	No. of Patients Giving Only Negative Results (B)	Total Specimens Examined in B	Percentage Patients Negative B/A
First	SP 5	34	0	0	0
	SP 10	38	2	4	5
	SP 20	40	1	1	3
Second	SP 5	34	4	8	12
	SP 10	37	5	8	14
	SP 20	40	1	2	3
Third	SP 5	30	7	21	23
	SP 10	38	9	18	24
	SP 20	41	12	24	29
Fourth	SP 5	33	13	32	39
	SP 10	38	15	31	39
	SP 20	40	18	35	45
Fifth	SP 5	32	7	21	22
	SP 10	39	10	21	26
	SP 20	37	9	17	24
Sixth	SP 5	32	10	28	31
	SP 10	36	9	16	25
	SP 20	38	7	16	18

There is no significant difference between the three groups. All were positive on admission. In all three the percentage of negative examinations rose steadily: 11–14% in the first month, 18–29% in the second, 35–46% in the third, until it reached 48–57% in the fourth month—that is, shortly after the three-months course of chemotherapy. It subsequently fell to 31–46% in the sixth month.

The results are similar when analysed in terms of the proportion of patients for whom all examinations were negative for tubercle bacilli throughout a month. The proportion of negative cases rose to 39–45% in the fourth month, and fell subsequently to 18–31% in the sixth month.

Streptomycin Sensitivity

Strains isolated on admission, and subsequently at least once a month, were tested for streptomycin sensitivity. The technique employed was the same as that previously reported.

All strains isolated before the start of chemotherapy showed sensitivity similar to that of the standard strain H37Rv. The results in succeeding months are set out in Table VIII and shown graphically in the Chart. As in the previous report, the results are designated by the resistance ratio (R.R.)—the ratio of the minimum concentration of streptomycin to which the tubercle bacilli of the patient are sensitive, to the corresponding figure for the standard strain H37Rv. There was some indication in the previous trial that where the resistance ratio is less than eight the strain

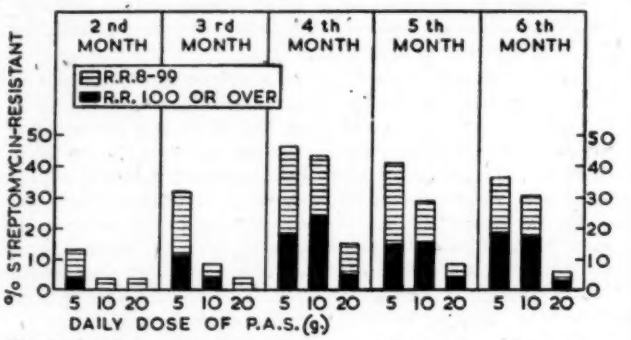


Chart showing percentage of cases with streptomycin-resistant strains in succeeding months after treatment started. All patients were treated for three months with daily streptomycin, 1 g., and P.A.S., 5, 10, or 20 g.

may be considered "sensitive"; accordingly the categories in this analysis are "sensitive" (less than eight), "moderately resistant" (8–99), and "strongly resistant" (100+). The result recorded in Table VIII for each case is that for the specimen with the highest degree of streptomycin resistance in the respective month.

In the first three months differences appear between the group receiving only 5 g. of P.A.S. and the other two groups: in the third month 32% of SP 5 cases had resistant strains, against 8% in the SP 10 group, and 4% in the SP 20 group. Subsequently the figures rise in both the SP 5 and SP 10 groups, and the percentage of resistant strains remains very low only in the group treated with 20 g. P.A.S. Thus the percentage of resistant cases in the fourth month was 47% in the SP 5 group, 43% in the SP 10, and only 15% in the SP 20; in the fifth month the corresponding figures were 41%, 28%, and 8% respectively; and in the sixth month 36%, 30%, and 7%. The difference between the group on the high P.A.S. dose and the others is even greater if we include only those strongly resistant. The conclusion must be that the dose of 20 g. of P.A.S. is much more effective in preventing or delaying the emergence of streptomycin resistance than doses of 5 or 10 g.

If only the cases giving strongly resistant strains are considered, in the SP 20 group of 42 patients there was only one such case; several cultures gave the same result. In the SP 10 group of 39 patients there were six cases: in four of these strongly resistant strains were isolated on several occasions; in a fifth there was an isolated one, followed by a strain with R.R. 8; in a sixth a single resistant strain was isolated in the sixth month. In the SP 5 group, among 34 patients there were seven cases: five were repeatedly highly resistant; in a sixth there was an isolated resistant culture, followed by a sensitive one; in a seventh, again, a single resistant strain in the sixth month. If these results are grouped for highly resistant strains, in 4 of the 14 cases it was an isolated observation, and in two of the four reversion to sensitivity or to R.R. 8 was observed.

Reversion to sensitivity was observed much more often in respect of moderately resistant strains, and in all three groups. In the SP 20 group there were six cases with moderately resistant strains: in five of them it was a single observation; in two of the five, sensitive strains were isolated subsequently. In the SP 10 group there were eight cases, and reversion to sensitivity was observed in seven of them. In the SP 5 group there were nine cases: five reverted to sensitivity, one other had a single resistant strain, and in three several resistant strains were isolated. If these results

TABLE VIII.—*Streptomycin Resistance in the Three Treatment Groups, in Successive Months after the Start of Treatment*

Month After Treatment Started	Group	Total* Examined (Cases)	Cases Giving Negative Cultures	Cases with Positive Cultures Examined for Sensitivity		Streptomycin-resistance Ratio† (Highest Recorded During the Month)					
						Less than 8 (Sensitive)		8–99 (Moderately Resistant)		100+ (Strongly Resistant)	
				No.	%	No.	%	No.	%	No.	%
First	SP 5	28	0	28	100	27	96	1	4	0	0
	SP 10	33	2	31	100	30	97	1	3	0	0
	SP 20	34	1	33	100	32	97	1	3	0	0
Second	SP 5	27	4	23	100	20	87	2	9	1	4
	SP 10	35	5	30	100	29	97	1	3	0	0
	SP 20	38	1	37	100	36	97	1	3	0	0
Third	SP 5	26	7	19	100	13	68	4	21	2	11
	SP 10	33	9	24	100	22	92	1	4	1	4
	SP 20	34	12	22	99	21	95	1	4	0	0
Fourth	SP 5	30	13	17	100	9	53	5	29	3	18
	SP 10	36	15	21	100	12	57	4	19	5	24
	SP 20	37	18	19	99	16	84	2	10	1	5
Fifth	SP 5	29	7	22	100	13	59	6	27	3	14
	SP 10	35	10	25	100	18	72	3	12	4	16
	SP 20	33	9	24	100	22	92	1	4	1	4
Sixth	SP 5	32	10	22	100	14	64	4	18	4	18
	SP 10	32	9	23	100	16	70	3	13	4	17
	SP 20	37	7	30	99	28	93	1	3	1	3

* The total includes all with negative cultures throughout the month, or with positive cultures of which at least one was examined for sensitivity. Excluded are those for whom no specimen was available and those for whom no specimen in the respective month was fully examined.

† The ratio of the minimum concentration of streptomycin to which the tubercle bacilli of the patient are sensitive, to the corresponding figure for the standard strain H37Rv.

are grouped for moderately resistant strains, reversion to sensitivity was observed in 14 of the 23 cases, and in four others a single resistant culture was isolated.

It is interesting to consider whether the continuation of chemotherapy after the first three months may have affected the streptomycin sensitivity. Resistant strains were isolated from 3 of the 14 patients who had further chemotherapy. One, on 5 g. of P.A.S., was resistant from the second month of treatment; another was resistant from the beginning of the fourth month, but treatment had been stopped at the end of the third month, and was not resumed till the end of the fourth; in neither of these cases, therefore, was the continuation of chemotherapy responsible for emergence of resistant strains. In a third case (No. 27) chemotherapy was continued throughout the six months; cultures were negative from the first until the fifth month, when strains with R.R. over 16 were isolated.

In this series it is difficult to relate the clinical results to the emergence of streptomycin resistance, since improvement was observed in so high a proportion of cases, and the proportion developing streptomycin resistance was relatively low. Furthermore, as in previous series, resistance was observed most frequently in those most acutely ill: strongly resistant strains were isolated from 5 of 20 patients acutely febrile on admission—average temperature, 100° F.+ (37.8° C.+)—from 6 of 45 patients not acutely febrile but with gross cavitation, and from 3 of 46 other patients. The combined results for all three treatment groups are given in Table IX.

TABLE IX.—*Radiological Results Related to Streptomycin Resistance and to Condition on Entry*

Clinical Condition	Streptomycin-resistance Ratio*	Total	Results at 6 Months. *X*-ray Assessment				Deaths
			Improvement		No Change	Deterioration	
			3+ or 2+	1+			
Temp. 100° F.+ (37·8° C.+)	Less than 8	8	5	2	0	1	0
	8–99	7	2	3	2	0	0
	100+	5	0	3	0	0	2
Temp. less than 100° F. but cavitation +	Less than 8	32	15	14	2	1	0
	8–99	7	4	3	0	0	0
	100+	6	3	1	2	0	0
Others	Less than 8	34	22	9	3	0	0
	8–99	9	5	3	1	0	0
	100+	3	2	1	0	0	0
Total†	Less than 8	74	42	25	5	2	0
	8–89	23	11	9	3	0	0
	100+	14	5	5	2	0	2

* Highest recorded at any time in the six months.

† For two cases that showed considerable improvement, and one with moderate improvement, sensitivity results are not available after the first month.

P.A.S. Sensitivity

The results of P.A.S.-sensitivity tests can conveniently be considered for all groups together, since very few resistant strains were isolated. The technique was similar to that employed for streptomycin-sensitivity tests. All but one were sensitive before the start of treatment. Strains from 87 patients (32, 28, and 27 in the SP 20, SP 10, and SP 5 groups respectively) were tested for P.A.S. sensitivity after treatment started; in the second month strains from 48 cases were tested, in the third 42, in the fourth 36, in the fifth 43, and in the sixth 46.

After the first month P.A.S.-resistant strains were isolated from three cases only. In two, both on 20 g. of P.A.S. daily, this was a single observation, with R.R. 40 (in the second month in one case, in the third month in the other); later strains were sensitive. The third case, in the SP 5 group, had a moderately resistant strain (R.R. 16) before treatment started; the only other culture tested was in the fifth month, and gave an R.R. 33; the streptomycin sensitivity was normal throughout.

Discussion

Emergence of drug-resistant organisms is one of the limiting factors in the present increasing range of antibacterial agents. Since the first demonstrations of the development of streptomycin-resistant organisms in pulmonary tuberculosis, ways have been sought to prevent this potentially dangerous change in character of the infective organism. One of the most effective ways found has been the association of P.A.S. with streptomycin, a daily dose of 20 g. of the sodium salt reducing the risk considerably. However, this high dose produces much gastric discomfort, and the investigation reported here was undertaken to determine if smaller doses of P.A.S. would be equally effective in reducing the risk of streptomycin resistance.

Three groups of patients with similar pulmonary disease (acute rapidly progressive bilateral pulmonary tuberculosis) received for three months 1 g. of streptomycin daily and 20, 10, or 5 g. daily of the sodium salt of P.A.S. Allocation to one or the other of the three groups was made by random selection, and the three were observed and treated in similar conditions. It was found that clinical results of treatment were uniformly good in all three groups: in general condition, temperature, and sedimentation rate, changes were similar; the same applies to the proportion

of cases becoming tubercle-negative and to the *x*-ray changes. Similar numbers in the three groups became suitable for collapse therapy.

Results of streptomycin-sensitivity tests, however, show clear differences between the groups; in the first three months very few of the cases on 10 or 20 g. of P.A.S. developed drug-resistant strains, whereas of those on only 5 g. one in three had resistant strains in the third month. Subsequently the percentages of resistant strains rose in both the groups on small doses of P.A.S., and remained low only in the group on 20 g. daily: in the fourth month the proportion of resistant cases was 47% in the SP 5 group, 43% in the SP 10, and only 15% in the SP 20; these differences persisted in subsequent months. There is no doubt that the dose of 20 g. is much more effective in preventing emergence of streptomycin resistance than are doses of 10 or 5 g., and that in adults the higher dose should be administered if it is tolerated. The clinical significance of these results is discussed elsewhere in this issue by Daniels and Bradford Hill (1952).

Other methods of preventing emergence of streptomycin resistance have not been investigated here, though one at least has been reported to be most effective. Administration of streptomycin every third or fourth day reduces the risk of emergence of streptomycin resistance and, it is claimed, without loss of clinical effect; combination of this regime with daily administration of P.A.S. reduces the risk even further (Veterans Administration, 1949–50).

Summary

A series of 115 patients with acute progressive bilateral pulmonary tuberculosis unsuitable for collapse therapy were studied in a clinical trial of streptomycin and P.A.S. All were treated for three months with 1 g. of streptomycin daily; in addition, 42 were given 20 g. of P.A.S. daily (SP 20), 39 had 10 g. (SP 10), and 34 had 5 g. (SP 5). Patients were assigned to one or another treatment group by random selection.

Gastro-intestinal disturbance was infrequent (12–15%) and mild in the two groups on lower doses of P.A.S.; in the group receiving 20 g. of P.A.S. the incidence was 52%.

The radiological assessment of change at the end of six months shows no difference between the three groups. The proportion showing improvement was 87–88%. No differences were found between the groups in respect of changes in temperature, sedimentation rate, general condition, or bacterial content of sputum.

Analysis of results of streptomycin-sensitivity tests show significant differences between the groups. In the third month 32% of SP 5 cases had resistant strains, against 8% in the SP 10 group and 4% in the SP 20 group. Subsequently the figures rise in both groups on lower doses, and remain very low in the SP 20 group. In the fourth month the proportion of resistant cases was 47% in the SP 5 group, 43% in the SP 10, and 15% in the SP 20. In the sixth month the corresponding figures were 36%, 30%, and 7%.

Reversion to sensitivity was observed frequently, in all three groups, in cases with moderately resistant strains.

REFERENCES

Daniels, M., and Hill, A. Bradford (1952). *British Medical Journal*, 1, 1162.
Medical Research Council Investigation (1950). *British Medical Journal*, 2, 1073.
Veterans Administration (1949-50). Minutes of 7th, 8th, and 9th Streptomycin Conferences. Washington.

Americans have started a national matching plan for placing new interns in hospital appointments. Students apply for internships and visit hospitals. Students and hospitals send confidential "ratings" to a national committee, which then matches them, and the student receives the internship he wants if the hospital's rating of him is satisfactory.

CHEMOTHERAPY OF PULMONARY TUBERCULOSIS IN YOUNG ADULTS

AN ANALYSIS OF THE COMBINED RESULTS OF THREE MEDICAL RESEARCH COUNCIL TRIALS

BY

MARC DANIELS, M.R.C.P., D.P.H.

Member of the Tuberculosis Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, C.B.E., Ph.D., D.Sc.

Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

During the period 1947 to 1951 three trials of chemotherapy of pulmonary tuberculosis in young adults were made under the direction of the Medical Research Council's Streptomycin in Tuberculosis Trials Committee. The first of these trials was designed to assess the efficacy of streptomycin itself. At that time the drug was available in only very small quantities, and it was thus possible to contrast the patients given streptomycin with similar patients treated by rest in bed only (M.R.C., 1948). In the second trial the newly discovered drug P.A.S. was brought under study, and its effects when used either alone or in combination with streptomycin were compared with the results given by streptomycin alone. It was clearly proved that the dose of 20 g. of P.A.S. daily would frequently prevent the development of streptomycin-resistant organisms (M.R.C., 1950). However, this dose often produced undesirable side-effects in the patient—nausea and vomiting—and a third trial was therefore set up to determine whether smaller doses of P.A.S. (5 or 10 g. daily) would be as effective as 20 g. in preventing the emergence of streptomycin-resistant strains. With the completion of this third trial (M.R.C., 1952) it is now possible to consider together the results of all three investigations.

The three trials were all designed in the same way. Clinicians and pathologists of several hospitals co-operated. The patients admitted to the trial had to conform to a particular definition (acute progressive bilateral pulmonary tuberculosis, believed to be of recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15–30); after acceptance by a panel the cases were randomly allocated to one or another treatment group; in each trial the different treatment groups were treated and observed concurrently; the clinical and radiological examinations and record-keeping were

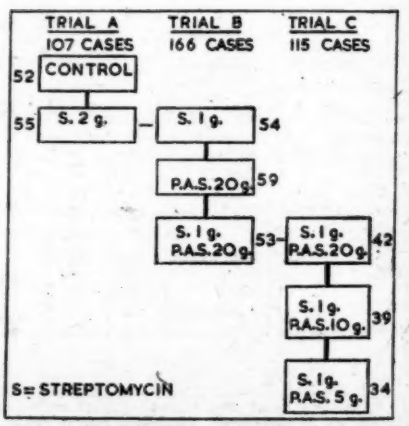


FIG. 1.—Diagram showing groups involved in the three trials.

made according to a plan previously agreed by all concerned; and, finally, the results of each trial were analysed by the Tuberculosis Research Unit of the Medical Research Council.

The groups involved in the three trials are shown in Fig. 1. There were 107 cases in Trial A, 166 in Trial B, 115 in Trial C: a total of 388 cases. An important feature of each study was that the groups on different treatments were observed concurrently. On the other hand, although the three trials took place at different points of time, a comparison between the non-concurrent groups is justifiable, since the methods of study were so similar and the type of case, as defined, remained the same. Also a link between the successive trials was deliberately introduced: Trial A and Trial B each had a group treated with streptomycin only (though in the first the daily dose was 2 g. and in the second 1 g.); Trials B and C each had a group treated with streptomycin, 1 g., and P.A.S., 20 g., daily. This "overlap" of a similarly treated group from one trial to the next should reveal whether it is fair to make comparisons between differently treated patients in the different trials.

Larger numbers are made available by bringing the three trials together. The main objects of this analysis are therefore: (1) to compare the clinical results of the different treatments employed in the three trials; (2) to analyse the effect of different treatments on streptomycin sensitivity; and (3) to assess the clinical significance of streptomycin resistance.

Comparability of Cases in the Three Trials

In Table I are given data, for each of the three trials, concerning the condition of patients before treatment started. The results are shown diagrammatically in Fig. 2. The analysis shows that the groups are very similar, though there is a suggestion that the cases admitted were somewhat less acute in successive trials. The proportion with average evening temperature of 100° F. (37.8° C.) or more in the pre-treatment observation week was 28% in Trial A, 27% in Trial B, 18% in Trial C; 7% were afebrile in Trial A, 10% in Trial B, and 17% in Trial C. The figures for sedimentation rate show a similar trend. Gross cavitation was found in 58% of patients in Trial A, compared with 52% in Trial B and 53% in Trial C. These differences are small enough to justify comparisons of results, but the question of initial condition will be referred to in respect of certain analyses.

TABLE I.—*Condition Before Treatment Started. Comparison of Patients in Three Trials*

Condition on Admission to Trial		Trial A		Trial B		Trial C	
		No.	%	No	%	No.	%
Total cases		107	100	166	100	115	100
Average evening temperature in first week	Afebrile	7	7	16	10	19	17
	Less than 99° F. (37·2° C.)	31	29	50	30	30	26
	99–99·9° F. (37·2–37·75° C.)	39	36	55	33	45	39
	100° F. + (37·8° C.+)	30	28	45	27	21	18
Sedimentation rate (Westergren)	0–10	0*	0	3*	2	2	2
	11–20	5	5	6	4	8	7
	21–50	36	34	67	41	50	43
	51+	65	61	89	54	55	48
X-ray: gross cavitation		62	58	87	52	61	53

* Examination not done in one case.

Results: Radiological Assessment

The most important measure of clinical results for each of the trials is the radiological assessment of changes between the condition just before treatment started and the condition six months later. The data for each of the eight groups are brought together in Table II. In Table III and Fig. 3 the two groups treated with streptomycin only (A2 and B1) have been combined; so also have the two groups receiving streptomycin plus 20 g. of P.A.S. (B3 and C1), and the groups receiving streptomycin plus 5 or 10 g. of P.A.S. (C2 and C3). Table II reveals, it is important to note, that in each of the pairs thus grouped together the results were strikingly similar. In other words, there is good evidence of a constancy of conditions in these three trials—ample justification, therefore, for adding groups together and for making cross-comparisons between the trials.

The results given in Table III show clearly a gradation in the frequency of improvement, from 33% for the cases treated by rest in bed only (the original comparative group) to 56% for those treated by P.A.S. alone, 71% for those treated by streptomycin alone, and, finally, nearly

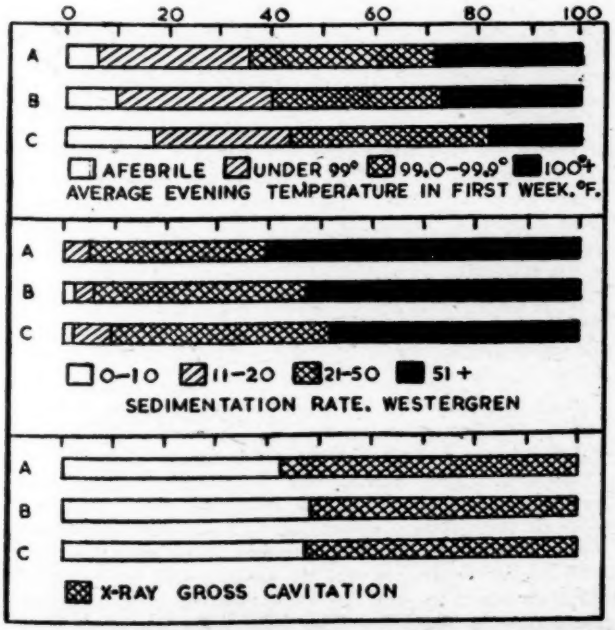


FIG. 2.—Condition before treatment started. Comparison of patients in three trials.

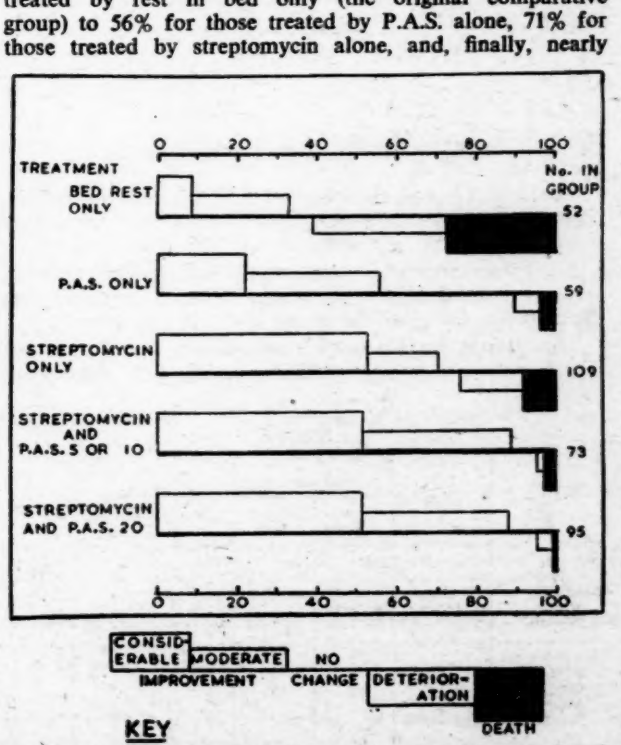


FIG. 3.—*X*-ray assessment at six months. Combined results of three trials.

TABLE II.—*Radiological Assessment at Six Months: Results in Three Trials*

Trial Group	Treatment (Daily Dose)		Total		Improvement				No Change		Deterioration		Death	
	Streptomycin	P.A.S.			Considerable		Moderate							
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A1	Nil	Nil	52	100	4	8	13	25	3	6	18	34	14	27
A2	2 g.	Nil	55	100	28	51	10	18	2	4	11	20	4	7
B1	1 g.	Nil	54	100	30	56	10	18	3	6	6	11	5	9
B2	Nil	20 g.	59	100	13	22	20	34	20	34	4	7	2	3
B3	1 g.	20 g.	53	101	27	51	19	36	3	6	3	6	1	2
C1	1 g.	20 g.	41*	100	22	54	14	34	4	10	1	2	0	0
C2	1 g.	10 g.	39	100	19	49	15	38	4	10	1	3	0	0
C3	1 g.	5 g.	34	100	19	56	11	32	2	6	0	0	2	6

* *X*-ray films of one patient not available.

TABLE III.—*Radiological Assessment at Six Months: Results in Three Trials*

Trial Group	Treatment (Daily Dose)		Total		Improvement				No Change		Deterioration		Death	
	Streptomycin	P.A.S.			Considerable		Moderate							
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A1	Nil	Nil	52	100	4	8	13	25	3	6	18	34	14	27
B2	Nil	20 g.	59	100	13	22	20	34	20	34	4	7	2	3
A2, B1	1 or 2 g.	Nil	109	100	58	53	20	18	5	5	17	16	9	8
C2, C3	1 g.	5 or 10 g.	73	101	38	52	26	36	6	8	1	2	2	3
B3, C1	1 g.	20 g.	94*	99	49	52	33	35	7	7	4	4	1	1

* *X*-ray films of one patient not available.

TABLE IV.—*Radiological Assessment at Six Months Related to Clinical Condition on Entry*

Condition on Entry	Treatment	Total		Improvement				No Change		Deterioration		Death	
				Considerable		Moderate							
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Acutely febrile	S only	34	100	11	32	6	18	2	6	6	18	9	26
	S + P.A.S.	34	100	12	35	12	35	3	9	4	12	3	9
Not acutely febrile but but with gross cavitation	S only	39	100	18	46	11	28	3	8	7	18	0	0
	S + P.A.S.	65	100	32	49	26	40	6	9	1	2	0	0
Others	S only	36	99	29	80	3	8	0	0	4	11	0	0
	S + P.A.S.	68	100	43	63	21	31	4	6	0	0	0	0

S = Streptomycin.

90% for those on combined treatment with streptomycin and P.A.S.

Clearly, all groups receiving either P.A.S. or streptomycin, or both, showed results very much better than the groups treated by rest in bed alone.

All groups receiving streptomycin had similar numbers showing considerable improvement (52–53%), results very much better than for the group given P.A.S. alone (22%).

The groups treated with streptomycin and P.A.S. had significantly greater numbers improving and significantly less deteriorating than those treated with streptomycin only. Deterioration (including those with a fatal ending) occurred in only 5% of those on combined therapy, against 24% in patients on streptomycin alone. In view, however, of the indication in Table I that cases were rather less severe in the later trials than in the earlier, the comparison between groups on combined therapy and those on streptomycin alone has been related to the condition before treatment started; the data are set out in Table IV. It is clear that the differences already observed apply regardless of initial condition.

It will also be seen that among the groups on combined chemotherapy the radiological results are almost identically the same whether they received 5, 10, or 20 g. of P.A.S. (see Tables II and III).

TABLE V.—*Radiological Assessment at Six Months: Men and Women*

	Total		Improvement				No Change		Deterioration		Death	
			Considerable		Moderate							
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
All cases:												
Men	175*	99	69	39	51	29	21	12	18	10	16	9
Women	212	100	93	44	61	29	20	9	26	12	12	6
All cases on chemotherapy:												
Men	154*	99	68	44	45	29	20	13	13	8	8	5
Women	181	100	90	50	54	30	18	10	13	7	6	3

* *X*-ray films of one patient not available.

Results in Men and Women.—Of male patients, 12% were in the early group treated by rest in bed only, 17% were on P.A.S. alone, 24% on streptomycin alone, and 47% on streptomycin plus P.A.S. Of the corresponding female patients 15% were on rest in bed, 14% on P.A.S. alone, 32% on streptomycin alone, and 40% on combined therapy. These proportions are fairly similar. The results for men and women separately, for all groups, and for all groups on chemotherapy—that is, excluding the control group—are shown in Table V. The small difference in favour of the women is not statistically significant.

Results of Sputum Examination

After radiological assessment the effect of chemotherapy on bacterial content of sputum is one of the most important measures of efficacy. The results for five groups are set out in Table VI. They show the same gradation of results as did the *x*-ray examinations, and again there is no significant difference between the groups on combined therapy but with different amounts of P.A.S.

TABLE VI.—*Sputum Examination: Results From Three Trials*

Treatment Group	Total Cases in Trial	Cases Sputum-Negative Throughout 3rd Month		Cases Sputum-Negative Throughout 6th Month	
		No.	%	No.	%
Rest in bed only	52	1	2	2	4
P.A.S only	59	5	8	4	7
Streptomycin only ..	109	16	15	17	16
Streptomycin +P.A.S. 5 or 10 g.	73	16	22	18	25
Streptomycin + P.A.S. 20 g.	95	27	28	22	23

Streptomycin Sensitivity Related to Treatment

For the purpose of the analysis of streptomycin sensitivity the results have been set out in four groups:

S2: The group in Trial A, treated with streptomycin only, 2 g. daily (55 patients).

S1: The group in Trial B, treated with streptomycin only, 1 g. daily (54 patients).

SP 5/10: Groups in Trial C, treated with streptomycin 1 g. daily plus P.A.S. 5 or 10 g. (73 patients).

SP 20: Group in Trials B and C treated with streptomycin 1 g. daily plus P.A.S. 20 g. (95 patients).

The grouped data are shown in Table VII and represented graphically in Fig. 4. In each successive month there is a clear gradation in results, from the highest percentage resistant in the S2 group to the lowest in SP 20. The differences are very striking, especially in respect of the proportion with strongly resistant strains (R.R. 100+); in the second month the proportion was 35% in the S2 group, 16% in the S1, 2% in the SP 5 or 10, and *nil* in the SP 20 group. In the fourth month it was 78% in the S2 group, 45% in the S1, 21% in the SP 5 or 10, and 4% in the SP 20.

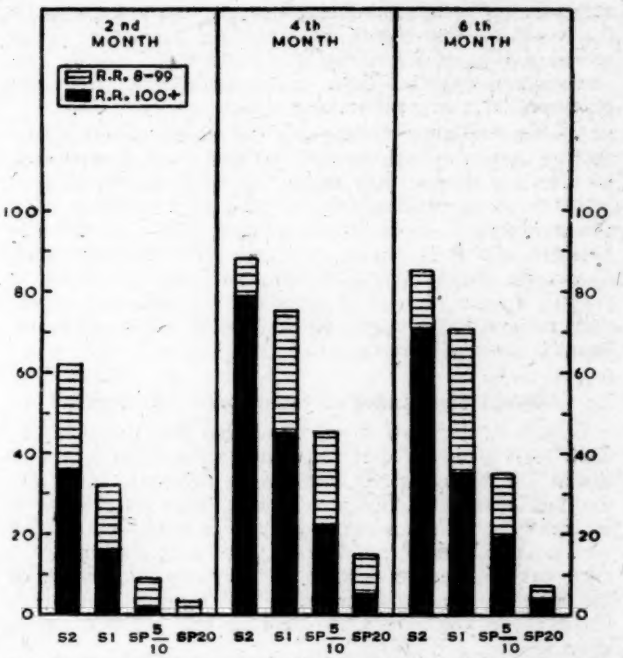


FIG. 4.—Percentage of cases with streptomycin-resistant strains in second, fourth, and sixth months after treatment started. Results from three trials. S2=Daily streptomycin 2 g. S1=Daily streptomycin 1 g. SP5/10=Daily streptomycin 1 g.+P.A.S. 5 or 10 g. SP20=Daily streptomycin 1 g.+P.A.S. 20 g.

The great difference between those receiving streptomycin only and those receiving streptomycin plus 20 g. of P.A.S. has been previously noted and discussed. So also has the difference between those receiving low doses of P.A.S. (5 or 10 g.) and those receiving 20 g. of P.A.S. daily. It is important, however, to note from the present analysis that, though the effect of 5 or 10 g. of P.A.S. is less than that of 20 g. in preventing emergence of streptomycin resistance, it is nevertheless quite considerable. Among those who received 5 or 10 g. of P.A.S. in addition to 1 g. of streptomycin

TABLE VII.—*Streptomycin Resistance in Successive Months after Start of Treatment: Results from Three Trials*

Month After Treatment Started	Treatment Group	Total Cases with Positive Cultures Examined for Sensitivity		Streptomycin-resistance Ratio* (Highest Recorded During the Month)					
				Less than 8 (Sensitive)		8–99 (Mod. Resistant)		100+ (Strongly Resistant)	
		No.	%	No.	%	No.	%	No.	%
First ..	S2	24	100	24	100	0	0	0	0
	S1	44	100	41	93	3	7	0	0
	SP 5 or 10	59	100	57	97	2	3	0	0
	SP 20	77	100	76	99	1	1	0	0
Second ..	S2	26	100	10	38	7	27	9	35
	S1	43	99	29	67	7	16	7	16
	SP 5 or 10	53	100	49	92	3	6	1	2
	SP 20	75	100	73	97	2	3	0	0
Third ..	S2	28	101	8	29	5	18	15	54
	S1	47	100	15	32	15	32	17	36
	SP 5 or 10	43	100	35	81	5	12	3	7
	SP 20	55	100	51	93	3	5	1	2
Fourth ..	S2	23	100	3	13	2	9	18	78
	S1	40	100	10	25	12	30	18	45
	SP 5 or 10	38	100	21	55	9	24	8	21
	SP 20	52	100	45	86	5	10	2	4
Fifth ..	S2	26	101	3	12	2	8	21	81
	S1	40	100	11	27	13	33	16	40
	SP 5 or 10	47	100	31	66	9	19	7	15
	SP 20	60	100	54	90	3	5	3	5
Sixth ..	S2	21	99	3	14	3	14	15	71
	S1	34	99	10	29	12	35	12	35
	SP 5 or 10	45	101	30	67	7	16	8	18
	SP 20	58	99	54	93	2	3	2	3

* The ratio of the minimum concentration of streptomycin to which the tubercle bacilli of the patient are sensitive, to the corresponding figure for the standard strain H37Rv.

daily, the proportion producing strongly resistant strains by the fourth to sixth month was only half that in the group receiving 1 g. of streptomycin without P.A.S. It is also noteworthy that in those receiving P.A.S. resistance developed at a somewhat later date.

Another important finding was the more frequent reduction of drug resistance in cases on combined therapy than in cases on streptomycin alone. In 5 of the 12 patients (42%) receiving streptomycin plus 20 g. of P.A.S. daily from whom resistant strains were isolated, the final cultures obtained in the six months were sensitive. Corresponding figures for the SP 5 and SP 10 groups are 13 out of 30 (43%), while in the group receiving 1 g. of streptomycin daily without P.A.S. only 4 out of 39 cases (10%) had subsequently sensitive cultures.

Clinical Significance of Streptomycin Resistance

In each of the trials it was found that the clinical results were least good in the cases with streptomycin-resistant strains. It was, however, difficult to dissociate this from the fact that streptomycin resistance was observed most frequently in patients most severely ill on admission. There was some indication, nevertheless, that streptomycin resistance was of some importance in determining the course of the disease. The amalgamation of data from the three trials makes it possible now to analyse this problem more effectively.

For the analysis set out in Table VIII, the results of streptomycin-sensitivity tests have been combined for 163 cases from four groups: those receiving streptomycin only and those receiving streptomycin plus P.A.S., 5 or 10 g. The percentage with resistant strains is so low in the groups receiving 20 g. of P.A.S. that their inclusion would weight the figures excessively with those for sensitive strains.

Of the 44 patients who were acutely febrile on admission, 27, or 61%, later produced strongly resistant strains, compared with 40% of the 63 not acutely febrile but with gross cavitation, and 21% of the 56 others.

Looking first at the results for all cases it is obvious that results were worst in those who produced strongly resistant strains at any time: 16% of them died, and no deaths occurred in the others; 36% died or deteriorated, against only 2–5% of the others; 55% improved, compared with 88–95% of the others. There is little difference between those with sensitive strains and those with moderately resistant strains, though the results slightly favour the former.

To assess the effect of initial condition in relation to the sensitivity results, the cases have been divided into three groups according to clinical condition on entry, and the results then related to sensitivity tests within each of those groups.

High fever has been taken as the main indicator of a severe condition on admission. The 10 deaths that occurred were all in the group of 44 patients who were acutely febrile before treatment started. But it will be noted that these deaths were all in those 27 who produced strongly resistant strains—a fatality rate of 37%; furthermore, only 11 of the 27 in this group improved, against 13 of the 17 others. The results were less good in those with moderately resistant strains than in those remaining sensitive: three of ten in the former group showed considerable improvement, compared with six of the seven in the latter. The difference is significant.

Among patients not acutely febrile on admission, but having gross cavitation, the only deterioration observed was in those with strongly resistant strains. Improvement was seen in 60% of these, compared with 94–96% of the others. There is no difference between those remaining sensitive and those with moderately resistant strains.

Among patients who were neither acutely febrile nor had gross cavitation, again the only deterioration observed was in those with strongly resistant strains, and in this group improvement was seen in 75%, compared with 94–97% of the others. Here again there is no difference between those remaining sensitive and those with moderately resistant strains.

Summarizing this analysis, it can be said that the relatively poor results in those who became strongly drug-resistant were not due solely to their initial severe condition. Among those acutely ill at the start of treatment the results were markedly worse in those who became strongly drug-resistant than in the others. In other clinical groups also the worst results were in the group with strongly resistant strains; 9 out of 37 deteriorated, and none of the 82 others, but the difference is less great than in those acutely febrile. Moderate drug resistance appears to be of much less clinical significance than resistance at higher levels.

Discussion

The discovery of streptomycin six years ago, and later of other specific drugs for tuberculosis, has changed radically many concepts of treatment and prognosis of this disease. To evaluate these drugs and determine how they can be used most effectively has been the task of many workers since that time. A series of chemotherapy trials organized by the Medical Research Council has contributed to that end. It

TABLE VIII.—*X-ray Assessment at Six Months Related to Clinical Condition on Entry and Streptomycin Resistance. Combined Results (from Three Trials) for Patients who Received Streptomycin Alone or Streptomycin Plus 5 or 10 g. P.A.S., and for whom Sensitivity Results are Available from Specimens Taken after the First Month of Treatment*

Condition on Entry	Streptomycin-resistance Ratio*	Total		Improvement				No Change		Deterioration		Death	
				Considerable		Moderate							
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Acutely febrile (average evening temperature 100° F. (37·8° C.) or over during first week)	Less than 8	7	100	6	86	0	0	0	0	1	14	0	0
	8–99	10	100	3	30	4	40	1	10	2	20	0	0
	100+	27	100	5	19	6	22	2	7	4	15	10	37
	Total	44	101	14	32	10	23	3	7	7	16	10	23
Not acutely febrile but with gross cavitation	Less than 8	23	100	11	48	11	48	1	4	0	0	0	0
	8–99	15	101	7	47	7	47	1	7	0	0	0	0
	100+	25	100	11	44	4	16	4	16	6	24	0	0
	Total	63	101	29	46	22	35	6	10	6	10	0	0
Others	Less than 8	27	101	21	78	5	19	1	4	0	0	0	0
	8–99	17	100	12	70	4	24	1	6	0	0	0	0
	100+	12	100	8	67	1	8	0	0	3	25	0	0
	Total	56	100	41	73	10	18	2	4	3	5	0	0
All cases	Less than 8	57	101	38	67	16	28	2	4	1	2	0	0
	8–99	42	100	22	52	15	36	3	7	2	5	0	0
	100+	64	100	24	38	11	17	6	9	13	20	10	16
	Total	163	101	84	52	42	26	11	7	16	10	10	6

* Highest recorded during the 6 months.

is appropriate, at a time when claims are being made for other newly discovered drugs (Robitzek and Selikoff, 1952), to look back over the series of Medical Research Council trials and to attempt, by amalgamating the results, to define the potentialities and limitations of the two drugs investigated. Evaluation of new drugs in the future can the more profitably be set against the background of established knowledge.

The three main trials undertaken were concerned with the effect of streptomycin and then of P.A.S. in pulmonary tuberculosis. All three were based on comparison of concurrently observed treatment groups, the placing of each case in one or another treatment group having been made by random allocation. In the first trial the value of streptomycin was compared with that of treatment by bed rest alone; in the second, P.A.S. was assessed by comparing it with streptomycin alone and in combination with that drug; the third was designed to determine the smallest dose of P.A.S. which, in association with streptomycin, would delay or prevent emergence of streptomycin resistance. A well-defined form of pulmonary tuberculosis was chosen for these investigations and served throughout the trials, giving them a uniformity which has made possible the present review of the combined results. Analysis of the condition on admission of the 388 patients in these trials shows that the various treatment groups are very similar in this respect, and the overlap of similarly treated groups from each trial to the next provides further justification for considering as one whole these three investigations, which took place at different points of time.

Radiologically all groups treated with streptomycin or P.A.S., or both, fared much better than the group treated by bed rest alone. Of the groups on chemotherapy, those treated with P.A.S. alone fared least well; results were much better in all groups treated with streptomycin, and best in those receiving P.A.S. in addition to streptomycin. Among the latter, the radiological results were the same whether the daily dose was 5, 10, or 20 g. of sodium P.A.S. Similar results apply to sputum conversion in the various treatment groups. It is clear that, on this assessment alone, the best chance of getting quickly effective action with streptomycin in pulmonary tuberculosis lies in its use with P.A.S.

Analysis of the levels of drug sensitivity adds weight to these findings. Streptomycin resistance developed more rapidly and more frequently in patients receiving streptomycin alone than in those treated with streptomycin plus P.A.S. In the fourth month after the start of treatment the proportion of cases with highly resistant organisms was 78% in the group treated with 2 g. of streptomycin daily, 45% in those on 1 g. of streptomycin daily, 21% in those treated with 1 g. of streptomycin plus 5 or 10 g. of P.A.S., and only 4% in those receiving 20 g. of P.A.S. with 1 g. of streptomycin. Further, reversion to drug sensitivity was seen frequently in cases on combined therapy, but relatively rarely in those treated with streptomycin only.

Though since 1946 much information has been obtained concerning emergence of streptomycin-resistant strains—and this has generally been assumed to worsen the prognosis—assessment of the clinical significance of bacterial drug resistance has been difficult. Certainly the best results were seen in patients who did not develop resistant strains, but on the whole these patients were at the start of treatment less ill than those from whom resistant organisms were later isolated. Many patients with streptomycin-resistant strains continue nevertheless to improve—whether under the influence of continued treatment or by their own resources is not clear. It is known also that drug-resistant organisms may be excreted into the bronchi from one lesion while other lesions in the same lung harbour streptomycin-sensitive bacilli (Canetti and Rocher, 1950). Because of the many complexities it has been difficult in relatively small investigations to judge the weight of this factor in prognosis. The present analysis has made it possible to disentangle some of the elements.

The relatively unfavourable prognosis in patients with highly resistant organisms was found to be due only in part to the fact that on admission they were very acutely ill; the clinical results were better in patients equally ill but who did not develop resistant strains. The analysis shows that, regardless of the initial clinical condition, the prognosis is, on the average, adversely affected by the emergence of strongly resistant organisms; moderate drug resistance seems to be of much less significance. Similar conclusions have been reached in a statement by the American Trudeau Society (1952).

It is true that in the groups on combined therapy there was no measurable difference in clinical results between those on 20 g. of P.A.S. and those on smaller doses, though drug resistance emerged in a greater proportion of the latter. However, the results in all groups on combined therapy were so good (87–88% showing radiological improvement) that differences are unlikely to show in groups of the size available. The one death that occurred in the 95 patients on 20 g. of P.A.S. and the two deaths in the 73 patients on lower doses were all three in cases from which strongly resistant strains were isolated. In view of the outstanding results in all groups on combined chemotherapy, and of the finding that even small doses of P.A.S. reduce appreciably the risk of drug resistance (compared with streptomycin alone), it is not possible to lay down absolute recommendations on dosage. The clinician must in each case weigh the lessened risk of drug resistance when high doses of P.A.S. are used against the greater digestive discomfort these doses may produce in the patient. The best working rule is probably to continue to give the maximum dose of 20 g. of sodium P.A.S. unless it is not tolerated by the patient.

The findings reported here relate to short-term results only (it is proposed later to analyse the results in the same cases at two years after the start of treatment), but they will help, it is believed, to determine the direction of work in connexion with new antibacterial agents in tuberculosis and possibly with drugs which may affect the host's reaction to the organism (Hart, Long, and Rees, 1952). Of the need of such scientific assessment as that produced by these trials there is no doubt: after each new advance assessment becomes the more difficult since each new drug must be measured against higher standards. The analysis of the results here presented has been made possible by the uniformity of the relatively small investigations from which they were derived, and by methods of planning which, now well proved, can be rapidly set in motion for the assessment of any new drugs.

Summary

The results of three Medical Research Council trials of chemotherapy in pulmonary tuberculosis have been amalgamated to provide material for a detailed analysis. 388 patients with similar forms of acute progressive bilateral pulmonary tuberculosis have been studied in these trials: 52 were treated by rest in bed only, 109 by streptomycin alone, 59 by P.A.S. alone, 73 by streptomycin plus 5 or 10 g. of P.A.S. daily, and 95 by streptomycin plus 20 g. of P.A.S. daily.

The results at six months after the start of treatment were much better in all groups on chemotherapy than in the group on rest in bed alone. They were much better in groups receiving streptomycin than in the group having P.A.S. only, and better in groups on combined therapy than in those on streptomycin alone. There was no apparent difference between the groups having different daily doses of P.A.S. plus 1 g. of streptomycin daily. There was no difference between the results in men and those in women.

The percentage of patients developing streptomycin-resistant strains was much higher in patients treated with

streptomycin only than in those on combined therapy; among the latter it was higher in those patients for whom the daily dose of P.A.S. was 5 or 10 g. than in those receiving 20 g. daily. The clinical significance of streptomycin resistance is discussed. In patients with a similar initial condition the results were worst in those who developed high degrees of drug resistance. Moderate drug resistance seems to be of less clinical significance.

This report is based on the work of clinical investigations directed first by the Medical Research Council Streptomycin in Tuberculosis Trials Committee, and then by a Joint Subcommittee composed of members from the parent committee and from the Research Committee of the British Tuberculosis Association. In these trials a large number of clinicians and pathologists have taken part. Their names appear in the report of each trial. To them the gratitude of the medical profession is due; only by their constant adherence to a centrally devised scheme and by a most remarkable team spirit on a large scale have these investigations been possible.

REFERENCES

American Trudeau Society (1952). *Amer. Rev. Tuberc.*, 65, 103.
Canetti, G., and Rocher, G. (1950). Chapter on Streptomycin Resistance, in *Advances in Tuberculosis Research*. Basle.
Hart, P. D'Arcy, Long, D. A., and Rees, R. J. W. (1952). *British Medical Journal*, 1, 680.
Medical Research Council Investigation (1948). Ibid., 2, 769.
—— (1950). Ibid., 2, 1073.
—— (1952). Ibid., 1, 1157.
Robitzek, E. H., and Selikoff, I. J. (1952). *Amer. Rev. Tuberc.*, 65, 402.

KERNICTERUS WITHOUT PREMATURITY OR BLOOD-GROUP INCOMPATIBILITY

BY

N. R. BUTLER, M.D., M.R.C.P. D.C.H.

AND

W. G. SPECTOR, M.B., M.R.C.P.*

(From University College Hospital, London)

Blood-group incompatibility was formerly believed to be a necessary precursor of kernicterus (Wiener and Brody, 1946; Claireaux, 1950). However, Aidin, Corner, and Tovey (1950), and also Zuelzer and Mudgett (1950) established the occurrence of kernicterus in premature infants without blood-group incompatibility. Zuelzer and Mudgett (1950) described a number of cases in which serologically compatible premature babies died of kernicterus, and also eight cases in which babies with birth weights of over 5½ lb. (2.5 kg.) showed presumptive evidence that no blood-group incompatibility existed, although none were first pregnancies. In only one of these eight instances does evidence for serological normality seem conclusive, in that direct Coombs tests were negative on the infants' cells, ABO groups were compatible, and no abnormal antibody was present in the maternal serum, either before or after delivery. Aidin, Corner, and Tovey (1950), although they included one baby whose birth weight was over 5½ lb. (2.5 kg.) in their group of kernicteric infants without blood incompatibility, gave no serological data for this case.

Thus, although the occurrence of kernicterus in the absence of blood-group incompatibility seems established in premature babies, only one unequivocal instance of this lesion occurring without either blood incompatibility or prematurity has yet been published. For this reason the following case is presented in which kernicterus occurred in a first-born infant, weighing 6 lb. 6 oz. (2.9 kg.) at birth, in whom blood-group incompatibility is believed to have been excluded, so far as is possible at the present day, by serological testing.

*Graham Scholar in Pathology in the University of London.

Case History

The patient was a first baby, born in the Obstetric Hospital at University College Hospital on July 2, 1951. The mother was a primipara aged 21. Her Wassermann reaction was negative, and there were no previous abortions or stillbirths, blood transfusions or other injections of blood or serum. The antenatal period was normal. Spontaneous labour occurred at 39 weeks and 1 day, followed by a normal vertex delivery. The first stage occupied three hours and the second stage 15 minutes. There was no foetal distress. The infant was a girl whose birth weight was 6 lb. 6 oz. (2.9 kg.). She was cyanosed at birth and remained so for several hours, but cried lustily at once and breathed normally within one minute. At the age of 3 hours the infant became restless, with an anxious facies and a high-pitched irritable cry. There was also pronounced inspiratory recession of the lower ribs with poor air entry at both bases. A diagnosis of intracranial irritation and atelectasis was made, due probably to a precipitate second stage of labour. The baby was transferred immediately to the resuscitation unit, where she was nursed in 50% oxygen and treated prophylactically with intramuscular penicillin, 100,000 units twice daily.

She remained irritable for the first 24 hours, but then her general condition improved, the cyanosis disappeared, and she began to suck. Oral feeding was started at 24 hours with expressed breast milk given three-hourly. At 36 hours jaundice first became apparent and deepened progressively for the next eight days, the spleen being just palpable from the third day onwards, when a peripheral blood count at 72 hours showed: red cells, 5,480,000; Hb, 110%; white cells, 12,800 (P. 63%, L. 27%, M. 7.5%, E. 2.5%). There were 1.5 normoblasts per 100 white cells. In view of the early onset of a deepening jaundice, with a negative direct Coombs test on the infant's cells (see Serology), a careful search was made for infection, but this revealed only a transient seropurulent umbilical discharge on the sixth day which disappeared 24 hours later but grew on culture *Bact. coli* and a penicillin-resistant *Streptococcus faecalis*. A course of oral sulphadimidine (total 4.5 g.) and chloramphenicol (total 1.7 g.) was therefore given for the next few days. The urine contained on one occasion 0.5 g. of albumin per litre, with occasional pus cells and three red blood cells per 1/6 microscopical field, with numerous epithelial and some granular casts. A transient apical systolic murmur was heard on the fifth and sixth days.

On the morning of the fifth day her general condition deteriorated rapidly with onset of head retraction and drowsiness, punctuated at intervals by athetoid movements of the limbs and occasional myoclonic twitchings. The anterior fontanelle was not full, but tone appeared to be increased in the limbs. A lumbar puncture produced only a small quantity of xanthochromic fluid, insufficient for chemical estimation, but with no excess of white blood cells or organisms in the Gram-stained centrifuged deposit. The baby became increasingly lethargic and refused to suck; intravenous fluids were given on the fifth day for 24 hours in the form of half-strength Hartmann's solution with 5% glucose. In view of the deepening jaundice, amino-acid supplements in the form of "pronutrin," 10 g., and choline chloride, 250 mg., were given daily by stomach tube, together with "becosym," 0.5 ml., and "synkavit," 10 mg. intramuscularly. By the sixth day the infant became febrile—101° F. (38.3° C.)—and was in a stage of opisthotonos and had two small generalized convulsions. All feeds had to be given by tube and were followed frequently by respiratory distress and cyanotic attacks, while large quantities of

blood-stained mucus were aspirated from the pharynx. From the sixth day to the tenth day the infant became progressively weaker and more jaundiced and the temperature fluctuated from 100 to 103° F. (37.8 to 39.4° C.). The central nervous signs remained unchanged, but on the tenth day breathing became irregular and gasping, and death supervened from respiratory failure on the morning of the eleventh day. Terminally the jaundice had subsided slightly, but was still deep in the skin and conjunctivae.

Serology

Infant.—Blood group O. Rh-positive (D+). Direct Coombs test negative at 72 hours of life and negative on infant's cells taken one hour after death. No abnormal blood-group antibodies discovered in infant's serum taken one hour after death, using cells from a panel of known Rh-positive and Rh-negative donors and other mixed genotypes.

Mother.—Blood group O. Rh-positive (D+). Indirect Coombs test negative, using mother's serum taken 11 days post partum and baby's cells taken one hour after death. Indirect Coombs test negative, using mother's serum taken 11 days post partum and cells from a known panel of Rh-positive and Rh-negative donors and other mixed genotypes. Indirect Coombs test negative, using mother's serum taken 14 days post partum (neutralizing with A-substance) and father's cells.

Father.—Blood group A. Rh-positive (D+).

Post-mortem Findings

External examination revealed the body of a full-term female infant weighing 2,530 g. Crown–heel length was 500 mm. and crown–rump length 335 mm. The skin showed definite jaundice, as did the conjunctivae. No maceration or oedema was present, the cord site was healthy, and the pupils were equal.

Respiratory System.—The pharynx, larynx, trachea, and main bronchi appeared normal and the airway was clear. The pleural spaces were free of fluid, but the pleural surface of both lungs showed scattered fresh petechiae. The lungs themselves were pale in colour and exhibited some surface emphysema. Their cut surfaces showed no evidence of consolidation, and portions from all lobes floated in formol-saline. The thymus was normal in appearance and free of haemorrhages.

Cardiovascular System.—The heart and great vessels were normal, apart from a few petechiae on the pericardial surface of the ventricles. The ductus arteriosus was barely patent and the foramen ovale widely patent.

Gastro-intestinal System.—Normal apart from congestion of the gastric mucosa.

The liver was of normal size, but was a deep olive green in colour. The surface was smooth and the lobular pattern normal for a neonate. The consistence appeared to be slightly firmer than is usual. The spleen weighed 10 g., which is within normal limits. The Malpighian follicles were not prominent but the appearances were otherwise normal, as was the consistence. The pancreas and adrenals were normal.

Biliary System.—The gall-bladder contained very viscous dark-green bile and the bile ducts were patent. No other abnormality was present. The kidneys showed "bilirubin infarcts"—that is, heavy deposits of bright-orange material arranged in linear streaks in the pyramids and as masses around the renal papillae.

Central Nervous System.—On opening the cranial cavity extensive haemorrhage was found localized to the temporal and parietal regions of both sides. This blood was for the most part still fluid, but its viscosity revealed that a good deal of its water content had been resorbed. The haemorrhage was both subarachnoid and subdural, and much of it remained adherent to the dura of the overlying cranial bones when these were reflected, the remaining blood covering the lateral aspect of the temporo-parietal lobes. Apart from one or two small areas of fraying in the tentorium, this membrane, together with the falx, dural sinuses, and vein of Galen showed no sign of damage, but some blood was present beneath the tentorium around the anterior and lateral margins of the cerebellar hemispheres. No bleeding into the ventricles of the brain had occurred. Section of the brain revealed numerous areas of bright-yellow pigmentation in its substance. This staining was visible in the basal ganglia in the thalamus, caudate, and lentiform nuclei, in the flocculus and dentate nucleus of the cerebellum, in the uncus and hippocampus, in the quadrigeminal nuclei, in the olives of the medulla, and in the floor of the fourth ventricle.

The diagnosis was traumatic intracranial haemorrhage, kernicterus, and jaundice.

Histological Examination

The lungs showed good aeration, with patchy emphysema and exudate in the lumen of some bronchioles, and small bronchi consisting of necrotic material, polymorphs, and mononuclear cells, without evidence of inflammation in the bronchial walls or lung substance. No evidence of erythropoiesis was present. The liver showed extensive "bile thrombi" in the biliary canaliculae and a mild degree of fatty infiltration. Haemopoiesis was practically absent and there was no evidence of hepatic necrosis or fibrosis. The spleen showed a good deal of broken-down blood pigment, but no more than is often found in the neonatal period. Scattered haemopoiesis of both red and white cells was present and lymphoid follicles were few in number, while the pulp was congested.

The kidney was congested and pigment granules were present, both lying free and within the epithelium of the collecting tubules. The pancreas, adrenals, and heart muscle showed no abnormality. Sections of the stomach wall revealed no evidence of inflammation. Paraffin sections of the affected portions of the brain, prepared in the standard way and stained with haematoxylin and eosin, showed no abnormality.

Discussion

The most widely accepted view of the pathogenesis of kernicterus is a dual-factor hypothesis in which the brain cells of the basal ganglia and other regions are rendered susceptible by some form of focal damage and then take up bile pigment from a coexistent hyperbilirubinaemia. In cases associated with blood-group incompatibility it has been suggested that this damage to brain cells occurs as a result of antigen-antibody reaction within the cells, or else is due to cellular anoxia caused by the presence of agglutination thrombi in the local capillaries (Wiener and Brody, 1946). Abnormally increased permeability of vascular endothelium in the brain due to capillary damage has also been postulated as a cause of kernicterus (Richards, 1951).

It now seems, however, that blood incompatibility is not an essential precursor of kernicterus (Aidin, Corner, and Tovey, 1950; Zuelzer and Mudgett, 1950), and that brain damage capable of making nerve cells permeable to bile pigment may also possibly occur as a result of hypoglycaemia, or even secondary to liver disease (Parsons, 1947), assuming that some relationship exists between liver damage and the central nervous system as in Kinnier Wilson's disease. Liver immaturity may certainly be a factor in the kernicterus of premature infants, many of whom have hyperbilirubinaemia and sometimes also hypoglycaemia (Norval, 1950) in the early neonatal period.

In the case reported here the major disorder, apart from kernicterus and jaundice, was subdural and subarachnoid haemorrhage. Assuming that prior damage to nerve cells, as discussed above, is necessary for kernicterus to develop, it may be that the brain cells of the infant were injured either as a result of compression caused by the haemorrhage within the cranial cavity, or by direct trauma or indirect damage following vascular injury incurred at the time of

birth. The severe jaundice appears, for want of evidence to the contrary, to have been of the "physiological" type, which is widely held to be a result of inadequate liver function. The presence of neonatal hepatitis was ruled out histologically and no significant infection was found anywhere.

Whatever the factors that led to kernicterus in the present case, it seems that a great deal of evidence now exists for the occurrence of symptomatic kernicterus as distinguished from a similar condition arising in conjunction with blood-group incompatibility. Thus a tentative aetiological classification of kernicterus may be put forward as (1) blood-group incompatibility; (2) a mixed group, comprising principally prematurity, and also severe infection, congenital anomalies, and maternal diabetes; and (3) cerebral damage following birth trauma.

Summary

A case of kernicterus is described in a full-term first-born infant in whom blood-group incompatibility was absent. The possible aetiology of the lesions is discussed, with particular reference to a coexistent intracranial haemorrhage.

Our thanks are due to Dr. B. E. Schlesinger and Dr. R. E. Bonham Carter, under whose care the baby was treated, and to Professor G. R. Cameron, for their advice. We are also grateful to Dr. Plaut, of the North London Blood Transfusion Service, for carrying out the serological testing.

REFERENCES

Aidin, R., Corner, B., and Tovey, G. (1950). *Lancet*, **1**, 1153.
Claireaux, A. (1950). *Arch. Dis. Childh.*, **25**, 61.
Norval, M. A. (1950). *J. Pediat.*, **36**, 177.
Parsons, L. G. (1947). *Lancet*, **1**, 815.
Richards, B. W. (1951). *Amer. J. ment. Defic.*, **55**, 529.
Wiener, A. S., and Brody, M. (1946). *Science*, **103**, 570.
Zuelzer, W. W., and Mudgett, R. T. (1950). *Pediatrics*, **6**, 452.

A STUDY ON THE A FACTOR AS A CAUSE OF HAEMOLYTIC DISEASE IN PREMATURE BABIES

BY

SOMSAK PHANSOMBOON, M.B.

(From the Siriraj Hospital Medical School, Bangkok, Thailand)

AND

O. J. POLLAK, M.D., Ph.D.

(From the Department of Pathology, Quincy City Hospital, Quincy, Mass., U.S.A.)

The view that anti-A and anti-B, as well as anti-Rh, can cause haemolytic disease of the newborn has been the subject of much controversy. The most common arguments against this view are based on the presumption that the abnormally increased titre of anti-A or anti-B antibody is the result of non-specific stimulation rather than a true iso-immunization such as occurs in the Rh system. Wiener (1951) thought that all the alpha and beta antibodies were of heterogenetic origin.

In recent years such arguments have lost some of their force because of accumulating evidence that there exist at least two varieties of A and B antibodies—namely, the complete (bivalent) and incomplete (blocking, immune, or univalent) ones. The behaviour of incomplete A and B antibodies is comparable to that of Rh blocking antibodies (Boorman and Dodd, 1946; Polayes and McNally, 1948; Witebsky, 1948, 1949; Hubinont, 1949; Wiener *et al.*, 1949).

This report is designed to furnish additional evidence of sensitization to the A factor as a cause of foetal erythroblastosis resulting in premature birth and neonatal death.

Materials and Methods

Cord blood from the affected babies was examined for the A, B, M, N, C, D, E, c, and e antigens; red- and white-cell counts, and differential and haemoglobin estimations were also performed. The serum was titrated for the A, B, and Rh antibodies, and the icterus index was determined. Gross post-mortem examinations were also made on the infants, followed by histological studies.

The blood of the parents was examined for the same blood-group antigens; the mother's serum was tested for anti-A, B, Rh, Kell, S, Le^a, and Fy^a agglutinins, and, in addition, titrations were carried out upon it for complete and incomplete A and B antibodies.

Four methods were employed to detect and titrate the antibodies: (1) the conglutination method of Wiener *et al.* (1947), (2) the trypsinized red-cell method (Morton and Pickles, 1947), (3) the anti-human-globulin test of Coombs *et al.* (1945), and (4) the neutralized serum method of Witebsky and Engasser (1949). Methods 2 and 3 were modified so that they could be applied to the ABO system.

Case 1

A white woman aged 19, a primigravida, was admitted to the department of obstetrics and gynaecology, Quincy City Hospital, because of irregular labour pains in about the 33rd week of gestation. Menstruation had begun at the age of 11, the cycle being 26 to 30 days, with periods lasting from four to six days. She was married in September, 1949, and strongly denied abortion prior to this pregnancy. To the best of her knowledge she had never felt menstrual molimina except at the onset of the present gestation, and had never received any injection of or had been transfused with whole blood or with blood products. In childhood she had been vaccinated against whooping-cough and diphtheria.

Physical examination showed a pregnant woman weighing 179 lb. (81.2 kg.), without oedema, anaemia, or jaundice. Temperature, respiration, and pulse were within normal limits. Her blood pressure was 130/78, 120/80, and 120/80 mm. Hg on three consecutive days. A serological test for syphilis (Hinton) gave a negative result. The erythrocyte count was 4,800,000 per c.mm., haemoglobin 14.2 g.% and white blood cells 8,500 per c.mm.; the differential count was non-contributory.

Spontaneous delivery took place under anaesthesia and was uneventful. Five days after parturition the fasting blood sugar was estimated at 110 mg. per 100 ml. of blood. Urinary examination for casts, albumin, blood, and sugar gave negative results.

The baby, a boy, was born on June 13, 1950, and weighed 4 lb. 4 oz. (1,920 g.); he had no deformity. The umbilical cord and sclerae were reported to be moderately icteric. Cutaneous petechial haemorrhages were observed at the extremities. The heart sounds were normal, but there were diminished breath sounds in the left chest. The liver and spleen were not palpable. He was kept in an incubator at 90° F. (32.2° C.), the treatment consisting of injections of "crysticillin," 30 ml. of whole compatible blood, calcium gluconate, vitamin K, and nikethamide. He died after three days and seven hours.

His red-cell count was 3,800,000 per c.mm., haemoglobin 13 g.%, and white-cell count 18,000 per c.mm.; the differential count gave 1% promyelocytes, 2% myelocytes, 4% band forms, 37% segmented cells, 1% basophils, 9% eosinophils, 6% monocytes, and 40% lymphocytes. The stained

cord-blood smear showed 105 nucleated red cells (97 normoblasts and 8 erythroblasts) per 100 white cells. The icterus index was 56 units.

The necropsy confirmed the clinical findings of jaundice and petechial haemorrhages. A small amount of free blood was found in the pleural cavities. The upper lobe of the left lung was collapsed, while the others were normal. The liver and spleen weighed 80 and 8 g. respectively, being slightly enlarged. The heart appeared normal. Kernicterus was not observed in the brain substance. Microscopically, the liver, spleen, and kidneys showed excessive extramedullary haemopoiesis. The results of serological examinations of the family are shown in Tables I and II.

TABLE I.—*Case 1. Blood Groups of Family*

Subject	Blood Groups	Remarks
Mother ..	O M CDe/cDE Secretor	Anti-N, S, K, Le^a, and Fy^a; negative
Father ..	A_1 N CDe/cde ,,	
Baby	A_1 MN CDe/cde ,,	Born in June, 1950, male. premature; died

TABLE II.—*Case 1. Titration of Mother's and Baby's Sera*

Medium	Antigen						Remarks
	A_1 cde/cde		A_2 cde/cde		B cde/cde		
	Mother	Baby	Mother	Baby	Mother	Baby	
Saline ..	6,100*	—	1,000	—	600	—	Method 3, phase I
Plasma ..	41,000	—	3,100	—	1,300	—	Method 1
Trypsinized cells ..	66,000	—	4,100	—	2,000	—	,, 2
Coombs's serum ..	98,000	—	5,100	—	3,100	—	,, 3, phase II
Neutralized serum ..	5,100	4,100	0	0	0	0	Method 4

* This is a twofold dilution starting from 1:2 or 1:3 or 1:10. The reciprocal value of the highest serum dilution which gives a definite positive reaction is taken as the final titre. For simplification, in cases where the titre exceeds 500 it is recorded in round figures—e.g., 6,100 and 98,000 instead of 6,144 and 98,304, etc.
— = not tested. 0 = no agglutination.

Case 2

A white woman aged 26, a 3-gravida, was admitted shortly after delivery, at home, of her third child. Menstruation, regular, 30 days cycle, and lasting five to six days, started at the age of 13. The first two pregnancies were uneventful, and resulted in 1946 and 1948 in the birth of full-term babies weighing 7 lb. 14 oz. (3.6 kg.) and 6 lb. 11 oz. (3 kg.) respectively. Physical examination showed her to be a well-developed and well-nourished woman, without oedema, anaemia, or jaundice, and the body temperature, respiration, and pulse were within normal ranges. The blood pressure was 110/70 mm. Hg, and the serological test for syphilis (Hinton) was negative. Urine examination showed a trace of albumin without any casts. Three days after delivery the fasting blood sugar was 118 mg. per 100 ml. of blood.

The baby—a female—was born on July 8, 1950, without apparent congenital malformation, and weighed 2 lb. 13 oz. (1,280 g.). She looked moderately icteric and her general condition was poor. No haemorrhage or discharge of blood was noticed. The baby received the same treatment as in Case 1, but died within 10 hours of admission.

Her erythrocytes numbered 3,600,000 per c.mm., haemoglobin 13.4 g.%, white-cell count 19,500 per c.mm.; the differential count gave 1% promyelocytes, 1% myelocytes, 3% metamyelocytes, 4% band forms, 34% segmented cells, 1% basophils, 8% eosinophils, 5% monocytes, and 43% lymphocytes. A cord-blood smear showed 152 nucleated red cells (140 normoblasts and 12 erythroblasts) per 100 white cells. The icterus index was 46 units.

The necropsy failed to reveal evidence of bleeding but confirmed the jaundice. The upper lobe of the right lung was atelectatic, while the other lobes were generally normal. The liver and spleen were slightly enlarged and weighed 68 and 6 g. respectively. The heart did not show any significant pathological change. The brain weighed 280 g. and did not show kernicterus. On microscopical examination extensive extramedullary haemopoiesis was observed in the liver and spleen. Erythropoiesis continued to be markedly extravascular, apart from the clusters of nucleated red cells in the liver sinusoids.

The serological investigations are shown in Tables III and IV. The fact that the father and baby belonged to the intermediate group A_1–A_2 was ascertained by the difference in quantitative titration, shown in Table V.

TABLE III.—*Case 2. Blood Groups of Family*

Subject	Blood Groups		Remarks
Mother ..	O MN CDe/cde	Secretor	Anti-E, S, K, Le^a, Fy^a; negative
Father ..	A*. M CDe/cdE†	,,	
First baby ..	O MN CDe/cde	,,	Male, born in 1946; living and well
Second baby ..	‡	?	Female. born in 1948; living and well
Third baby ..	A*. M cdE/cde	?	Male, born in July, 1950, premature; died

* Intermediate A_1-A_2 type (see Table V).
† The father's genotype cannot be CDe/cde because his wife and two of the children have genes "cde" and one of them is of genotype cdE/cde.
‡ Unable to come for investigation.
? = Unidentified.

TABLE IV.—*Case 2. Titration of Mother's and Third Baby's Sera*

Medium	Antigen						Remarks
	A_1 cde/cde		A_2 cde/cde		B cde/cde		
	Mother	Baby	Mother	Baby	Mother	Baby	
Saline ..	1,500	—	160	—	128	—	Method 3, phase I
Plasma ..	2,600	—	320	—	256	—	Method 1
Trypsinized cells ..	4,100	—	500	—	320	—	,, 2
Coombs's serum ..	6,100	—	1,000	—	500	—	,, 3, phase II
Neutralized serum ..	1,000	770	0	0	0	0	Method 4

TABLE V.—*Quantitative Titration of Immune A antibodies with Red Cells of Intermediate A_1–A_2 Type*

Titre of Immune A Antibodies*	Red Cells of Father (Case 2)	Red Cells of Third Baby (Case 2)	Control A_1 Cells	Control A_2 Cells
1:32	+++	+++	++++	0
1:64	+++	++	++++	0
1:128 ..	++	+	++++	0
1:256 ..	++	+	+++	0
1:512 ..	+	±	+++	0
1:1,024 ..	+	0	++	0
1:2,048 ..	±	0	++	0
1:4,096 ..	0	0	+	0
1:8,192 ..	0	0	+	0

* One part of immune A serum is first neutralized with two parts of A–B substances. Dilutions were made in normal AB serum (undiluted).
0 = no agglutination. ± = weak agglutination. + = definite agglutination. ++ = strong agglutination. +++ = very strong agglutination. ++++ = extremely strong agglutination.

In addition, the sera from the two mothers were tested against a panel of O cells having the specificity for S(MN), Kell, Lewis, and Duffy antigens, all with negative results.

Discussion

Iso-immunization to the A_1 factor in a first pregnancy (Case 1) and to the A_1–A_2 factor (Case 2), resulting in premature birth and foetal erythroblastosis, is seldom recorded in the literature. That iso-immunization to the A–B factors with fatal consequences is not more frequently brought to light may be due to the following reasons: (1) The A–B factors are not generally accepted as a cause of severe foetal erythroblastosis. (2) More attention has in the last decade been focused on Rh incompatibility as a cause of foetal death. (3) Many

premature babies die very soon, so that serological and systematic investigations are not possible. Without such study, death in these cases is often recorded as due to prematurity and atelectasis.

Mild cases of erythroblastosis caused by the A–B factors in first and subsequent heterospecific pregnancies have been reported by Halbrecht (1944), Wiener *et al.* (1949), and Brancato (1950). Halbrecht introduced the term "icterus praecox," which is now widely accepted. Recently he stated that icterus praecox occurred not less frequently than the other forms of haemolytic disease, the proportion being 1 in 25 to 1 in 30 of heterospecific pregnancies (Halbrecht, 1951).

The argument that the mother in Case 1 might have had a previous missed abortion, coinciding with the time of expected menstruation and thus escaping her notice, deserves comment. In such a case the foetus could be only a few weeks old, and its blood group agglutinogens would probably not have developed enough to sensitize the mother. Mackenzie (1950), moreover, considered menstrual molimina to be one of the earliest presumptive signs of gestation.

The baby in Case 1 is known to have been a secretor. The secretor status of Case 2, however, cannot be stated definitely, even though the parents are both secretors, since we were unable to obtain sufficient material for the inhibition test. It is still a controversial matter whether the maternal A and B antibodies affect secretor babies or not. Levine (1946) assumed that only non-secretor babies are affected by those antibodies. On the other hand, Wiener *et al.* (1949), having found that secretor babies were also afflicted with haemolytic disease, concluded that such antibodies did not act directly on the tissue cells, but apparently produced damage through the blood stream, presumably by agglutinating the red cells and thus blocking the circulation. We have observed only one case in which a secretor baby is affected, and we cannot therefore offer an opinion. Further intensive and careful investigations on a large number of similar cases are necessary before a definite conclusion can be warranted. The real problem is rather that of finding out why all babies with appropriate blood groups do not suffer from haemolytic disease.

Summary

Two serologically and histologically proved cases are reported of iso-immunization to the A factor, resulting in the birth and neonatal death of infants suffering from erythroblastosis. In the first case, sensitization to the A_1 factor occurred in the first pregnancy of a young woman, and in the second case to the intermediate A_1–A_2 type in a third pregnancy.

In Case 2, differentiation between A_1, intermediate A_1–A_2, and A_2 is required, and is shown by the quantitative method.

The significance of serological investigation of premature babies is discussed.

We wish to express our thanks to Drs. E. Nathan and I. Edelstein for kind permission to study their private patients, to Miss Eda Deitsch, M.T., Miss Kathryn Crane, and Miss Alexandra Codakes for technical assistance, and to Dr. A. E. Mourant for suggestions and criticism.

REFERENCES

Boorman, K. E., and Dodd, B. E. (1946). *Nature, Lond.*, **158**, 589.
Brancato, G. J. (1950). *Amer. Dis. Child.*, **80**, 287.
Coombs, R. R. A., Mourant, A. E., and Race, R. R. (1945). *Brit. J. exp. Path.*, **26**, 255.
Halbrecht, I. (1944). *Amer. J. Dis. Child.*, **69**, 248.
—— (1951). *J. Pediat.*, **39**, 185.
Hubinont, P. O. (1949). *British Medical Journal* **2**, 574.
Levine, P. (1946). *Ann. N.Y. Acad. Sci.*, **46**, 939.
Mackenzie, L. L. (1950). *Amer. J. Obstet. Gynec.*, **60**, 941.
Morton, J. A., and Pickles, M. M. (1947). *Nature, Lond.*, **159**, 779.
Polayes, S. H., and McNally, J., jun. (1948). *Amer. J. clin. Path.*, **18**, 375.
Wiener, A. S. (1951). *J. Immunol.*, **66**, 287.
—— Hurst, J. G., and Sonn-Gordon, E. B. (1947). *J. exp. Med.*, **86**, 267.
—— Wexler, I. B., and Hurst, J. G. (1949). *Blood*, **4**, 1014.
Witebsky, E. (1948). Ibid., Special Issue No. 2, p. 66.
—— (1949). *Fed. Proc.*, **8**, 414.
—— and Engasser, L. M. (1949). *J. Immunol.*, **61**, 171.

A PECULIAR SYNDROME OF "BLADDER PARALYSIS" IN NATIVES OF SOUTH CENTRAL AFRICA

BY

M. GELFAND, M.D., F.R.C.P., D.P.H.

AND

E. E. BARNETT, M.B., F.R.C.S.Ed., D.T.M.&H.

(From the Salisbury Hospital (Native), Southern Rhodesia)

For some years in this hospital we have become increasingly aware of a form of bladder "palsy" in the male African adult with urinary bilharziasis, running as a rule a typical course of brief duration followed by complete recovery.

The patient is generally between the ages of 20 and 50, previously in good health, and first observes a fairly rapid inability to void urine. The difficulty increases over a day or more, less urine being evacuated with each effort. He next finds he cannot pass any at all, the bladder at this stage becoming grossly distended. All efforts to pass urine are without avail; but while he may have some pain, it is never severe or as discomfiting as is usual with other forms of retention. The next stage is one of dribbling or overflow incontinence, a few drops of urine issuing from the distended viscus. At this stage the patient generally seeks medical aid at the hospital, being admitted as a case of "acute retention." When seen the diagnosis usually made is one of obstruction due to a urethral stricture, an enlarged prostate, or perhaps a calculus. Yet a striking feature is the relative comfort and ease of the patient (Fig. 1) and the absence of anything to support an obstructive disturbance.

FIG. 1.—A patient with well-marked distension of bladder.

A small soft catheter can be passed without difficulty. Instead of encountering any form of obstruction or resistance, it will be found to pass with perfect ease into the bladder, which is then emptied. A little puzzled, one withdraws the catheter only to find that after some hours the bladder tumour appears again, the patient being totally unable to void, and so the catheter is again passed and the whole performance repeated. The patient is thus in a state which might best be described as *complete atony of the bladder*. He knows his bladder is full, but in spite of this he is not disturbed, and appears to be fairly comfortable. This stage lasts several days, and then the organ seems to regain its "tone" and a similar process in reverse to the onset denotes the stage of recovery. The bladder slowly appears to regain its former tone, the degree of retention becoming progressively less over a couple of days and the amount voided increasing.

The patient has now recovered, and as a rule recovery may be regarded as permanent. Occasionally, however, we have seen a relapse after a few weeks, the second attack being less severe and recovery more rapid; nevertheless, the same stages as already described are seen.

A Typical Case

An intelligent African male aged about 22 was admitted to the Salisbury Hospital on August 9, 1951, with acute retention with overflow of some two days' duration (Fig. 2).

For some years he had been aware of a terminal haematuria, but except for that he enjoyed good health. He denied ever having had venereal disease. Seven days before his admission he became aware of increasing difficulty in emptying his bladder, and in about five days could not pass any urine, though some did dribble away. He then reported at a clinic, where he was catheterized. As the retention reappeared he was admitted to hospital, where he was found to have a large bladder tumour with urine dripping from it. He seemed to be relatively comfortable in spite of the enormous distension of the viscus, but said he had some pain in the bladder itself.

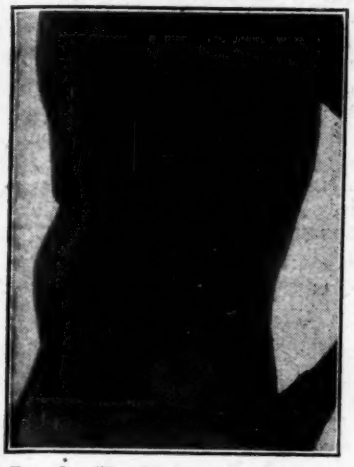


FIG. 2.—The bladder can be seen extending to above the umbilicus.

A soft rubber catheter (No. 8) entered the bladder with great ease, 18 oz. (510 ml.) of clear urine being evacuated. No sense of obstruction or difficulty was encountered then or on any of the subsequent occasions he was catheterized. All discomfort would disappear after the organ was emptied. He would get up and sit in the hospital grounds perfectly at ease until his bladder filled again. He would then be catheterized. He continued in this way until August 16, when he began to pass urine on his own accord. At first it was only a few ounces at a time, but next day it increased to about 8 oz. (227 ml.), though the bladder was never completely evacuated. After three days he had completely regained his former bladder function and was ready to leave hospital.

Urine could be made to flow from the bladder by manual pressure over the viscus, and would continue as long as the pressure was maintained. At no time did he mention any penile or perineal pain: he admitted the presence of hypogastric discomfort only when questioned.

The patient was a well-covered native; he could not speak English, but was intelligent, co-operative, and pleasant. We could not find or elicit at any time anything to suggest a neurotic. He was well coloured. A blood count showed: red cells, 5,000,000; haemoglobin, 90% (Newcomer); colour index, 0.9; white cells, 16,200 (neutrophils 78%, lymphocytes 20%, monocytes 2%). He was practically apyrexial during the course of his illness, the temperature occasionally rising to 99° F. (37.2° C.) in the morning. His pulse rate varied between 76 and 80 and the respirations from 16 to 20. The cardiovascular system was normal, the blood pressure being 130/80, and the fundi were clear. The lungs were normal on *x*-ray film; liver and spleen were not palpable on abdominal examination. The blood urea was 35 mg. per 100 ml. The nervous system was examined carefully and was found to be perfectly intact. There was no alteration in the reflexes. The motor power of the limbs was good and no sensory loss could be detected at any time. The cranial nerves were normal.

The urine showed a trace of albumin, and microscopical examination revealed a few epithelial cells but no leucocytes or blood. At a later examination there were a few leucocytes, plus red cells and ova of *Schistosoma haematobium*. *Bact. coli* was grown on culture. Rectal examination was negative, and a prostatic smear failed to show any significant organisms.

Cystoscopy disclosed a severe and diffuse bilharzial infiltration of bladder mucosa, the whole of which was covered with pale greyish mossy patches. The ureteric orifices were not seen. Intravenous pyelography done while the patient still had the disorder revealed a well-marked bilateral hydronephrosis typical of bilharzial disease.

His blood Wassermann reaction was negative. The cerebrospinal fluid was unfortunately not a clear tap, there being a little blood in the fluid submitted. Cell count: leucocytes 48 per c.mm.; red cells, 848 per c.mm.; chlorides, 740 mg. per 100 ml.; Nonne-Apelt negative; total proteins, 20 mg. per 100 ml.; no cells or organisms were seen in stained smears; the Wassermann reaction was negative.

Discussion

At no time in these cases were we able to find an obstructive lesion such as a stone, an enlarged prostate, a urethral stricture, or a congenital anomaly of the prostate or urethra. The easy passage of a soft rubber catheter with constant regularity also tends to dismiss a mechanical disorder.

At one time we were rather inclined to believe that these cases might be encephalitic in origin. If so, we would have expected some motor weakness or sensory changes in the lower limbs. A careful examination of these cases never revealed anything to support this condition. The cerebrospinal fluid findings were also disappointing. The Wassermann reaction was negative, and the cell count and so on were usually normal.

When we came to consider a hysterical state we were in difficulties, because this is one of the first suggestions that come to the mind. But the course of the illness in these cases is usually typical and runs true to type. It is not bizarre, nor does it vary from day to day as one would anticipate in a functional disorder. The palatal reflex is normal in these cases.

Could this be a bilharzial manifestation due to infiltration of the bladder with diffuse bilharzial lesions? All the cases so far encountered showed this disease in varying degree; but it must be admitted that, in any event, most Africans suffer from bilharziasis in this part of Africa. It may thus be purely coincidental.

Summary

A peculiar form of retention with overflow incontinence in the African male is described.

It appears in three stages—a short period of progressively increasing difficulty in micturition with some retention, followed by complete retention with overflow for several or more days, and the final or third stage in which the patient passes urine in increasing amounts until the function is restored completely.

No obstructive lesion could be found in these cases.

All cases so far suffered from bilharziasis, which, however, may be an incidental finding.

We would like to express our thanks to Dr. R. M. Morris for his criticisms and for his kind permission to publish this paper.

The addition of a magnetic iron stripe to 16-mm. film will produce a small revolution in education, according to Dr. David S. Ruhe, director of the Medical Audio-visual Institute of the Association of American Medical Colleges. The magnetic stripe is a recent technical development which allows amateur film producers to convert silent film footage into sound films cheaply and easily. Using the same procedure as the tape recorder, the stripe makes possible great flexibility in commentary. Medical teachers will be able to adapt sound stripes to different audiences. For example, a film used for medical students may be "erased" and re-recorded for use with a group of nurses. Cost of the magnetic iron stripe will be somewhat less than the titles of a silent film, and quality of sound on the magnetic film is excellent. The iron stripe is said to outwear the film to which it is applied.

RELIEF OF ACUTE LEFT VENTRICULAR FAILURE BY "PRISCOL"

BY

DAVID WHEATLEY, M.D.

The acute attack of left ventricular failure occurring with dramatic suddenness in the early hours of the morning cannot fail to impress itself upon those called to witness it.

Among the many typical features often seen in these attacks the extreme pallor of the patient is one of the most striking. Its persistence in lips and conjunctivae may have led others, as it has me, to call for a haemoglobin estimation, only to find the latter normal. The explanation lies in the intense peripheral vasoconstriction which constitutes an integral part of the pathogenesis of the condition (Fishberg, 1940; Wood, 1950). Whatever the initiating cause, it would appear likely that this vasoconstriction results in the sudden rise in blood pressure which precedes the attacks. To this, in turn, may be attributed the functional inabilities of the weakened left ventricle and the resulting pulmonary congestion. That these attacks most commonly occur in cases of hypertension lends weight to such speculation. Wherever the true explanation may lie, a therapeutic attempt to release this peripheral vasoconstriction would not seem out of place. The vasodilator tolazoline hydrochloride (" priscol "; 2-benzyl-imidazoline hydrochloride) was chosen for this purpose on account of its effectiveness and freedom from side-effects.

Braun and Fryd (1951) have studied the fall in blood pressure and peripheral venous pressure produced by priscol in various types of cardiac failure. These were most pronounced in cases of chronic cor pulmonale. However, they attribute these effects to peripheral venous dilatation.

Witham and Fleming (1951) have demonstrated the action of adrenaline, and Fowler *et al.* (1951) that of L-*nor*adrenaline, in reproducing many of the precipitating causes of acute pulmonary oedema. Priscol might, by its adrenolytic action, therefore also contribute to the relief of the condition, although its action against *nor*-adrenaline is slight (Freis *et al.*, 1951).

The following is a description of the cases in which priscol has been tried.

Acute Pulmonary Oedema: Intravenous Injection

Case 1.—A frail senile woman aged 85 developed congestive cardiac failure with pronounced peripheral oedema. No valvular lesion could be demonstrated, but hypertension of the order of 200/100 mm. Hg had been present for several years. For some time she had suffered from mild attacks of cardiac asthma, controlled by oral aminophylline. Regular mersalyl injections relieved the oedema, and an episode of auricular fibrillation was controlled with "digoxin." However, digitalization could not be continued, with any preparation, owing to vomiting; but fortunately there was no recurrence of fibrillation. Shortly afterwards she developed an attack of acute pulmonary oedema. When she was first seen the condition had been present for some six hours, and there was extreme respiratory distress with the usual signs of acute pulmonary congestion. The lips exhibited a pallor approaching the colour of parchment. The haemoglobin content of the blood a few days previously was 11.5 g. per 100 ml. (78%); the red-cell count being 3,900,000 per c.mm. Priscol, 1 ml. (10 mg.), was slowly injected intravenously. After the first 0.1 ml. had been given there was an immediate change in the colour of the lips to a bright cherry-pink, and the attack was relieved in four minutes. She was subsequently given priscol orally, 25 mg. twice daily; and in the ensuing six weeks there was no recurrence of left ventricular failure.

Case 2.—A 75-year-old lady had suffered from five attacks of acute pulmonary oedema in four months. These had been relieved by injections of morphine, but never in less than four hours after the injection. The present attack had started two to three hours before she was seen. Acute respiratory distress was present, her lips were somewhat cyanosed, and many bubbling rales and rhonchi could be heard all over both lung fields. No cardiac lesion could be detected (the patient had not been seen before), and blood pressure was 180/120 mm. Hg. Priscol, 1 ml. (10 mg.), was slowly injected intravenously. One minute later the lips had improved in colour and the blood pressure was 170/100 mm. Hg, but there was little relief of respiratory distress. Four minutes after the injection breathing was easier and blood pressure 180/110 mm. Hg. Five minutes after this the respiratory distress had been almost completely relieved and no rales or rhonchi could be heard with the stethoscope. The blood pressure was now 165/100 mm. Hg and the lips were a healthy pink colour. Three minutes later the improvement was maintained and the blood pressure was 175/100 mm. Hg. There was no recurrence of the attack, and she slept peacefully through the remainder of the night. In the morning her blood pressure was 165/110 mm. Hg.

Cardiac Asthma: Oral Administration

In addition to the acute cases described, priscol in doses of 25–50 mg. at night was administered to six patients who suffered from regular short attacks of nocturnal cardiac asthma. In these cases reliance had to be placed on the patients' account of the degree of relief experienced. In two cases there was complete relief, so that the patients slept the whole night through, whereas previously they had been awakened night after night in the early hours. In one there was partial relief, so that his attacks were reduced from half an hour to a matter of minutes. In one other case the drug could not be tolerated because of side-effects, and in the other two no relief at all was experienced.

Discussion

In the acute attack of pulmonary oedema a remedy is required which will give immediate relief. In my experience intravenous aminophylline, digoxin, and mersalyl have all proved extremely disappointing, and the only effective drug has been hypodermic morphine, resulting in extremely slow relief of symptoms, never in less than half an hour. It is felt that the rapid results obtained with intravenous priscol in the two cases described warrant a further trial of this drug. The longer-acting oral tablets may also have a place in the treatment of the milder forms of the condition.

REFERENCES

Braun, K., and Fryd, C. H. (1951). *Brit. Heart J.*, 13, 294.
Fishberg, A. M. (1940). *Heart Failure*, p. 149. Philadelphia.
Fowler, N. O., Westcott, R. N., Scott, R. C., and McGuire, J. (1951). *J. clin. Invest.*, 30, 517.
Freis, E. D., MacKay, J. C., and Oliver, W. F. (1951). *Circulation*, 3, 254.
Witham, A. C., and Fleming, J. W. (1951). *J. clin. Invest.*, 30, 707.
Wood, P. (1950). *Diseases of the Heart and Circulation*, p. 160. London.

A course in international medical law has been started in the faculty of medicine at Bordeaux University. This is the first result in France of an attempt to secure adequate protection for doctors in cases of ethical conflict. The aim is to translate moral principles into written law. In 1947 Italy created a chair of international medical ethics at the School of Military Medicine. Mexico and Havana followed suit, and Belgium's four medical faculties plan to do likewise. The Bordeaux course is to include instruction in international medical law in both peace and war. Considerable attention will be paid to the position of doctors in the armed Forces and in relation to prisoners of war.

Medical Memoranda

A Case of Ectopia Cordis Surviving Nine Hours

The condition of ectopia cordis was defined by Maude Abbott in 1915 (quoted by Blatt and Zeldes, 1942) as "a displacement so that the heart passes out of the thorax and comes to lie either upon the outer surface of the body or in the abdominal cavity." In 1818 Weese (quoted by Blatt and Zeldes, 1942) classified cases into three types—"ectopia cordis cum sterni fissura, ectopia suprathoracica, and ectopia subthoracica"—and the first known example is that of Haller's in 1706. In the most recent review of the literature Byron (1948) reports that of the 142 cases previously described 4 were suprathoracic or cervical, 81 were thoracic, 38 subthoracic or abdominal, 10 combined thoraco-abdominal, and 9 unclassified.

Blatt and Zeldes (1942), in an analysis of 53 cases, show that, of the three types of case, the cervical is incompatible with more than a few hours of life, and the abdominal has the greatest expectation of life (see Table).

Summary of Blatt and Zeldes's Cases

	Cervical	Thoracic	Abdominal	Thoraco-abdominal	Total
Stillborn	1	5	6	—	12
Lived less than 24 hours	1	10	2	—	13
Lived few hours—1 year	—	11	5	4	20
Lived over 1 year ..	—	2	6	—	8
	2	28	19	4	53

Abdominal cases have been described in which the patients lived to 10, 24, 36, and 37 years, the 36-year-old case being of interest as she survived four pregnancies. Another, of unrecorded age, was a most remarkable case described by Deschamps (approximately 1780) in which a soldier who had taken part in several campaigns died of suppurative nephritis, and at necropsy was found to have in place of an absent left kidney the heart in its pericardial sac. Probably the number of cases that have not been reported is small, as the condition is of great rarity, but there is at least one thoracic type in the museum of an English medical school, and possibly other specimens exist.

In a search among more recent publications five cases not included in Byron's (1948) review have been found, making, with the present case, 148 in all. Four of these are thoracic (Molinengo, 1939; Stephan, 1942; Ammal, 1946; Burton, 1947) and one cervical (Burton, 1947). Of these, Burton's are notable because of successful recovery after surgical treatment at 6 weeks and 12 years respectively. In his cervical case the heart was dissected from surrounding structures and lowered into the thoracic cage, and in both cases the sternal defect was made good by transplantation of the eighth and ninth right costal cartilages, after which muscles and skin were drawn together. Earlier operative cases quoted by Byron were reported by Cutler and Wilens in 1925, Bloch in 1927, and Hofmann in 1938. In the first three cases the infant survived operation for 11 hours, 22 hours, and 7 days, but skin sutures had to be released owing to the throttling of the heart. Hofmann's case succumbed during the replacement of the heart into the thoracic cavity.

In most cases pregnancy and delivery have been normal, although about 50% of the babies have been premature. There is usually no relevant family history.

A number of the cases have had other developmental anomalies, either single or multiple. In 1936 Wanstrom (quoted by Blatt and Zeldes) recorded a case with hydrocephalus, equinovarus, and spina bifida; and in the same year Puddu and Cammarella (also quoted by Byron) one with a meningocoele, hare-lip, hypophalangism of the right hand, umbilical hernia, and bilateral equinovarus. Although in some specimens the heart has been normal, a number have had intracardiac defects, including Fallot's tetralogy as in the present case. In Grieg's series (1926, quoted by Byron) there were 2 cases with trilocular hearts, 3 with bilocular hearts, 6 had two superior venae cavae, and 4 with multiple anomalies.

The following case is recorded because of the rarity of the condition.

CASE REPORT

The mother, a primipara aged 39, was admitted to hospital on July 28, 1950, at the 33rd week of pregnancy, on account of swelling of the ankles for the past month. She had been troubled by vomiting throughout pregnancy, and had had three attacks of "flu," the first within the first six weeks of pregnancy, followed for some weeks by a cough.

On examination her general condition was excellent, but there was moderate oedema of the ankles. Her blood pressure was 130/50, the fundus of the uterus was at 32 weeks, and the presentation a breech, which was subsequently converted to a vertex. There was no albuminuria. Her haemoglobin was 69% (10.2 g.% Haldane), blood group O Rh-positive, blood urea 32 mg. per 100 ml., with 80% standard urea clearance and a urinary urea of 3.9 g.% three hours after a dose of 50 g. of urea had been taken. The Wassermann reaction was negative. She was kept in bed, and by August 4 had rapidly developed a moderate hydramnios, which did not, however, progress far. Her blood pressure later rose to 180/120, though with no concurrent albuminuria, and she was given a surgical induction on August 25, followed three and three-quarter hours later by a normal delivery.

Photograph taken shortly after death.

The baby appeared to be full-term, breathed well, but was cyanosed. She had a bilateral hare-lip and a cleft palate. There was a circular defect, measuring approximately 1½ in. (3.8 cm.) across, in the mid-sternal region of the anterior chest wall through which could be seen part of the right lung beneath intact pleura, and through which ran the great vessels. The heart was entirely external (see illustration), and was covered only by pericardium. Owing to damage to the pericardial vessels during delivery a considerable amount of blood was lost, but the child was remarkably lusty, with at times only a mild cyanosis. She survived nine hours.

At post-mortem examination the presence of a cleft palate was confirmed. The two halves of the sternum had

failed to fuse in their entire length; the upper and lower parts of the separation being covered by skin. The only other extramediastinal abnormality was the presence of rudimentary clefts in place of the interlobar fissures of the lungs. The diaphragm was intact, and no abnormality was found in the abdominal viscera.

Dissection of the heart proved it to be of an advanced Fallot type, with a completely right-sided aorta, a large right ventricle with a tiny left ventricle, absence of the pars membranacea of the interventricular septum, and an infundibular pulmonary stenosis. The pulmonary artery was remarkable for its very low exit from the right ventricle, a considerable distance from the aorta, with no evidence of a previous arterial trunk. The right auricular appendage was enormously enlarged, the left very tiny, and the foramen ovale was patent. The pulmonary veins and venae cavae were normal, and the ductus arteriosus was very narrow and probably not patent after birth.

I wish to thank Mr. Trevor Barnett and Surgeon Rear-Admiral J. A. Maxwell for permission to publish this case; Dr. R. D. Clay, who performed the post-mortem examination; Dr. J. H. Moseley for helpful criticism and advice; and Sister E. Reay for the photograph.

ELEANOR J. WILSON, M.B., Ch.B.,
House-physician to Paediatric Department, St. Mary's Hospital, Milton, Portsmouth.

REFERENCES

Ammal, P. G. (1946). *Antiseptic*, 43, 420.
Blatt, M. L., and Zeldes, M. (1942). *Amer. J. Dis. Child.*, 63, 515.
Burton, J. F. (1947). *Arch. Surg.*, 54, 79.
Byron, F. (1948). *J. Thorac. Surg.*, 17, 717.
Molinengo, L. (1939). *Atti Soc. ital. Obstet. ginec.*, 35, 474.
Stephan (1942). *Arch. Gynäk.*, 173, 168.

Torsion of a Fallopian Tube

Torsion of a tube without an accompanying ovarian tumour is rare, and there appears to be no previous report of a case in association with uterine fibroids.

CASE REPORT

The patient was a housewife aged 39. After breakfast in bed on Sunday, March 11, 1951, she developed a cramp-like pain in the left iliac fossa, together with pain over the left buttock and outer side of the left thigh down to the knee. Blaming constipation, she took liver salts and emptied her bowels, but the pain remained and she vomited. Her doctor thereupon sent her to hospital with a tentative diagnosis of twisted ovarian cyst. On admission at 2 p.m. the pain and nausea continued. The patient said that menorrhagia lasting 8 days every 28 had been present for the previous year or two, but no dysmenorrhoea. L.M.P., February 19. She had had a normal confinement in 1940 and an abortion in 1942. Her previous health was good. Micturition was normal, but the bowels were constipated.

On examination her temperature was 97° F. (36.1° C.), pulse 84, respirations 20, and blood pressure 130/80. The urine was normal. The patient was pale and cold, but not shocked, and sat up without demur. The breasts were dry. The heart, lungs, nervous system, and legs were normal. There was a point of maximum pain and tenderness 2 in. (5 cm.) above the middle of the left inguinal ligament, and a soft mobile mass rose from the pelvis to 3 in. (7.5 cm.) above the symphysis pubis; the abdomen was otherwise normal. Vaginal examination showed that the cervix was softened; a firm tumour in the pouch of Douglas appeared continuous with the abdominal mass and cervix; the appendages were not defined. A twisted ovarian cyst seemed to be the most likely diagnosis, with pain referred to the left tubal "point." A fibroid undergoing torsion or pressing on the left ureter was also considered. In any case, laparotomy was indicated.

At 4 p.m., under general anaesthesia, a lower midline incision exposed a uterus enlarged with fibroids to the size of a four-months pregnancy. There was a soft fibroid in the fundus and a hard one filling the pouch of Douglas. The left uterine appendage was lying between fibroid and anterior abdominal wall, twisted clockwise through three-quarters of a circle at the junction of isthmus and ampulla. Both tube and ovary were swollen; the ampulla was dark red, and there was a stigma on the ovary. The torsion was easily corrected. The right appendage appeared normal. Total hysterectomy and bilateral salpingo-oophorectomy was carried out. No other abnormality was noted. The patient made a good recovery and had no further pain. She was ready for home in a fortnight, and when seen two months after the operation appeared to be very well.

Pathology.—The right tube and ovary were normal to the naked eye, but on section the ovary contained some cystic follicles. The left ovary was twice as big, measuring 2 by 1½ by 1 in. (5 by 4 by 2.5 cm.). The fresh cut surface of the stroma was wet, the oedema of acute congestion; there was no change in colour. It contained two corpora haemorrhagica, each ¼ in. (1 cm.) in diameter, the stigma connected with one of these denoting recent ovulation; also a few cystic follicles. The left tubal ampulla was twice as big as the right, and the wall showed congestion; the lumen was normal. The body of the uterus was enlarged with fibroids; the largest, occupying the pouch of Douglas, measured 4 in. (10 cm.) across, and the fibroid in the fundus showed cystic degeneration. The cervix was normal.

COMMENT

With regard to the distribution of pain, the standard works, such as Quain's (1909), state that the sensory fibres of the tube probably originate in the posterior roots of D 11 and 12 and L 1 and run to the tube in the ovarian plexus. Jefferson (1926) described a case of tubal torsion in which the pain was referred to the buttock, presumably along the lateral cutaneous branch of the posterior ramus of L 1. In the case reported here the pain was felt in the buttock, but it also extended down the outer side of the thigh to the knee. This area is innervated by the lateral femoral cutaneous nerve, which contains fibres from the anterior primary ramus of L 2, and also occasionally of L 1. This "high form" may have occurred here. The skin over the well-known tubal point mentioned above is supplied by the anterior branch of D 12. Another classical sign of a twisted tube, rigidity of the corresponding part of the rectus abdominis muscle, was not manifest, though it may have been obscured by the fibroid. De Soldenhoff (1949), although he prefers early excision, has quoted an older description of spontaneous cure in certain cases in which aseptic sloughing of the twisted tube occurred into the peritoneal cavity. This provides an unusual contrast to the behaviour of a strangulated appendix; the treatment of choice, however, is surgical.

I thank Dr. W. R. Addis for permission to operate on this case at Davyhulme Park Hospital, Manchester.

P. G. SEED, M.B., D.R.C.O.G.

REFERENCES

Jefferson, J. C. (1926). *British Medical Journal*, 1, 55.
Quain, J. (1909). *Elements of Anatomy*, vol. 3, Part 2, pp. 92, 141
de Soldenhoff, R. (1949). *British Medical Journal*, 2, 263.

Commenting on the rising cost of medical treatment in the United States, William S. McNary, chairman of the National Blue Cross Commission (the equivalent of the British Hospital Savings Association for voluntary health insurance), attributed it mainly to the health propaganda that leads Blue Cross subscribers to demand service in hospitals (*New York Times Supplement*, May 20). He said that much of the treatment these people receive in hospital was unnecessary. The question at issue, states the *New York Times*, is, "Who is to decide?" The subscriber has paid for medical attention, and is entitled to receive it. The Blue Cross was founded to give good care at low cost, and the paper considers that press propaganda helps the work of the organization.

Reviews

THE GROWTH OF TOWNS

The Making of our Towns. By Sir William Savage, M.D. (Pp. 189. £1 1s.) London: Eyre and Spottiswoode. 1952.

Sir William Savage is well known for his bacteriological researches, as a public health administrator, and as an expert on food-poisoning outbreaks. In this book he comes before the public for the first time as a historian, although some are aware that English history has been one of his interests for many years.

He has explored an almost untouched field, for until now there was no comprehensive history of the making and growth of British towns (London has purposely been excluded). This gap in historical knowledge Sir William Savage has filled. He starts from the beginning of things. In the first chapter he describes how the need for towns arose partly for security and partly for trading, and discusses the physical features, soil, situation, and water supply which determined the sites of towns. The towns in pre-Roman and Roman Britain are next described. When the Anglo-Saxons came they were at first rural, not town-dwellers, and many of the well-designed Roman towns, like Silchester, fell into decay; although the author surmises that this deterioration began during the latter stages of Roman occupation, because of crippling taxation inflicted from 284 A.D. onwards by the extensive reforms of Diocletian. The Anglo-Saxons did not begin to take to town life until 871 A.D. The growth of town government is narrated in Chapters 4 and 5.

Under Norman rule two important factors leading to the growth of new towns were the vicinity of a castle, thus securing protection by an over-lord, and the neighbourhood of a monastery. Baron, abbot, and bishop alike claimed tribute from the towns and the labour of their inhabitants. Counteracting this feudal sway was the growing power of the Crown; and many towns obtained royal charters and secured their independence. Apart from New Sarum (now Salisbury), laid out in the thirteenth century, all the planned towns in England and Wales—Hull, Winchelsea, Conway, Caernarvon, Beaumaris, Harlech, and Criccieth—were due to Edward I. The rest of our towns, including Liverpool, founded by King John, unfortunately, have grown unplanned, and it is only to-day—and then with many obstacles—that intelligent town-planning universally prevails.

Other chapters are devoted to life within the towns, industry which has greatly influenced their growth, developments in towns after mediaeval times, and seaports and seaside towns. The concluding chapter on the waxing and waning of towns shows how villages have grown into towns and towns become villages; former ports have lost their harbours, while others have been encroached on by the sea or even become submerged, like Dunwich. Many of our urban institutions have their roots in past ages, and many of our present economic problems were experienced in mediaeval and Tudor times.

Sir William Savage has so much to tell in the limited space of this book that he has only briefly touched upon public health and sanitary progress in English towns. Perhaps in a future work he will develop this theme.

The book is a most valuable contribution to historical knowledge of local government, and the copious lists of authorities cited at the end of each chapter show how the author has supplemented his personal investigations by wide reading. The book is illustrated by a charming reproduction of one of David Cox's paintings and by a number of diagrams and plans.

ARTHUR S. MACNALTY.

OPHTHALMOLOGICAL PAPERS

Transactions of the American Ophthalmological Society. Eighty-sixth Annual Meeting, Hot Springs, Virginia, 1950. (Pp. 702; illustrated. £4 17s. 6d.; to include *Ocular Toxoplasmosis*, by Michael J. Hogan (pp. 86, illustrated).) New York: Columbia University. London: Geoffrey Cumberlege. 1951.

Transactions of the American Ophthalmological Society covers the 86th annual meeting and fully keeps to the high level and scientific tradition which this somewhat exclusive society has undoubtedly earned. In commemoration of the centenary of the introduction of the ophthalmoscope, the volume begins fittingly with two historical papers—one on the early years of Helmholtz by the senior ophthalmological historian of America, Dr. Burdon Chance, and the other by Dr. Arthur J. Bedell on the period of intense activity which characterized the ten years following the invention of this instrument.

The other papers and discussions are scientific. Among the most interesting of them is a discussion introduced by Dr. David Cogan, of Boston, on ocular injuries by nuclear energy as seen in a comprehensive survey carried out on survivors of the atom bomb explosions in Japan during the last war. These included multiple injuries to the eyes and lids, kerato-conjunctivitis from ultra-violet and ionizing radiations, thermal burns of the cornea and retina, retinitis proliferans, and, as a delayed manifestation, radiational cataract, of which ten cases were found among people who were within one kilometre of the hypocentre of the explosion and were unprotected except by wood or plaster. The latent period before subjective symptoms became obvious is about two years. This is supplemented by a description by Dr. von Sallman of experimental studies on the somewhat similar lenticular changes that follow *x*-radiation.

Medical ophthalmology is represented by several papers, all of considerable value, on diabetic retinopathy in juvenile cases and in pregnancy, the correlation of retinal changes with the surgical treatment of hypertension, the ocular changes following aortic-pulmonary anastomosis for congenital heart disease, the relation of the endocrine glands to the development of cataract, and the ocular manifestations of multiple sclerosis. Surgical subjects are represented, among others, by the description of a new and very simple suction apparatus for use in cataract extraction and a discussion on the dynamics of this type of operation, total penetrating keratoplasty, the treatment of the retracted eye socket, and the severe iritis which follows the accidental introduction and retention of foreign bodies such as surgical lint in the anterior chamber during intraocular surgery. There are also several papers on the diagnosis and treatment of various types of squint.

Therapeutics is represented by an able and detailed summary by Dr. Alan Woods of the value and limitations of cortisone and A.C.T.H. in ocular diseases, and an interesting paper by Dr. E. W. Hansen suggests that the mucocutaneous eruption generally known as Stevens-Johnson's disease (erythema multiforme exudativum) is an example of an inherent or acquired sensitivity to drugs. Altogether this is a stimulating and interesting volume.

It is a curious thing that the recognition of the occurrence of a disease which, although probably rare in Britain, is relatively common in other countries, should have been delayed until 12 years ago, and it is all the more curious when the condition is caused by an easily recognized parasite and gives rise to a typical and dramatic clinical picture. Since its recognition by Wolf and his collaborators in the U.S.A. in 1938, toxoplasmosis has excited much attention, not least among ophthalmologists, for one of the most common, easily seen, and distinctive features of the condition is the destructive chorio-retinitis by which it is so often characterized. An instructive monograph summarizing most of our knowledge of this condition appeared some time ago from the pen of Binkhorst, of Holland. *Ocular Toxo-*

plasmosis is a second and equally excellent work. In its 86 pages Dr. Hogan gives a well-written summary of the known facts concerning the toxoplasma, the clinical and particularly the ocular manifestations in human infections, the histopathology, the clinical and serological diagnosis of the condition, and its treatment. This is accompanied by a description of six clinical cases, a summary of the 78 cases recorded in the literature with ocular manifestations, and the 13 (including two of the author's) which had come to pathological examination, as well as a description of the results of experimental infections in animals undertaken by the author.

How the protozoon parasite, which is found in a large number of mammals and birds, is transmitted to man is unknown. Since the congenital form of the disease acquired from the mother is the only form associated with ocular lesions, this alone is considered. The toxoplasma enters the eye from the blood stream, and the usual primary lesion in this organ is a destructive retinitis or chorio-retinitis. It is interesting that in his experiments on rabbits infected by injection into the carotid artery Hogan found lesions only in the uveal tract, a distinction probably depending on the difference in retinal blood supply. The damage done to the eye depends on the stage of foetal development at the beginning of the disease. Early infection results in numerous symptoms resulting from extensive damage to the central nervous system and the eye—nystagmus, ocular deviations of various types, unilateral or bilateral microphthalmos, papilloedema, iridocyclitis with synechiae, cataract, optic atrophy, and opacification of the vitreous. Infections during the antenatal or post-natal period are characterized mainly by the development of chorio-retinitis. When a positive diagnosis cannot be made by recognition of the protozoon in the body fluids or in tissues removed for biopsy, Hogan finds the most satisfactory serological tests to be the complement-fixation test and the methylene-blue test. It is interesting that he concludes that, although clinical experience gives rise to little optimism, animal experiments would justify the use of large doses of sulphonamides in treatment. Antiprotozoal drugs and a formidable list of antibiotics have been found quite useless.

STEWART DUKE-ELDER.

LIFE IN HARMONY

Das Leben. By Professor August Bier. (Pp. 212. M. 12.50.) Munich: J. F. Lehmanns Verlag. 1951.

August Bier was born in 1862, was professor of surgery in Berlin until 1932, and died in 1949 at the age of 87. He was one of the greatest of German surgeons, and his name will always be associated with the use of venous congestion for the treatment of inflammation and especially for the relief of pain. But his interests extended far beyond the realm of surgery, and in many ways he resembled our own John Hunter. For 30 years he maintained a tract of woodland in which he could observe Nature under her own conditions, and this study became the absorbing interest of his life.

He held that all natural processes can be explained as parts of one great harmony, and in his search for the basis of this harmony he went back to the Greek philosophers. Heraclitus and Hippocrates were his heroes, and much of *Das Leben* is devoted to their writings. To them everything was transient, nothing remained unchanged, and therefore our observations should be directed to the nature of the changes, their causes, and their effects. In modern medicine and in modern physics he sees a full confirmation of their views, and his analysis is of great interest.

He must have been a man of great charm, and perhaps this may best be felt in a passage from his book, though, alas, much of its charm is of necessity lost in translation :

"I stand on a fine warm summer's day in a luscious meadow and absorb the lovely picture which surrounds me. Many kinds of grass, clover, and other herbs grow side by side, flowers bloom in endless variety, and butterflies hover around. Grasshoppers and other insects play their cheerful music, bees and flies hum and beetles drone. Frogs hop in the grass, storks strut, thrushes and other birds lie hidden. The many mole-hills show what an active animal world is hidden underground. In the evening stags, does, and hares emerge from the meadow. Ten thousand individual beings, separate, conflicting, live together in harmony. Yet the meadow is one organic unit and itself depends upon its soil. Wet means illness, drought brings death."

HENRY SOUTTAR.

BEFORE AND AFTER MARRIAGE

Marriage: A Book for the Married and about to be Married. By Kenneth Walker, F.R.C.S. With foreword by Professor F. A. E. Crew, F.R.S., F.R.C.P. (Pp. 136. 8s. 6d.) Published for the British Social Biology Council by Secker and Warburg, London. 1951.

A large number of books on marriage and sex have been written in recent years, and Mr. Kenneth Walker justifies this addition to the literature by pointing out that others in the field are not sufficiently comprehensive to supply the answers to all the questions which couples about to be married, or recently married, may ask. He thereby sets himself an enormous task, and the fact that he comes very near to achieving it within the space of 127 pages calls for congratulation. It is inevitable, of course, that each problem receives only brief mention, but the author succeeds in giving useful comment on nearly every one which can arise between masturbation in infancy and finding a house or dealing with a mother-in-law, and even after that. Many books of this kind have been written by women, and often those with a mission: this is different in that it is not only written by a man but by one whose practice has given him a wider and less prejudiced outlook on these matters.

The author is careful to explain that some of his views, and particularly those on premarital chastity, are personal, and without the official sanction of the society sponsoring the book. Professor Crew rightly emphasizes that the mixture of fact and opinion means that lay readers—for whom the book is intended—should be able to distinguish between the two. They should be sufficiently educated not only to follow a concise account of anatomical, physiological, and psychological phenomena, but also to assess for themselves the author's expressions of opinion on human behaviour, using them as points for argument rather than absolute guides to conduct. Such people will read this work with profit.

T. N. A. JEFFCOATE.

COMPELLING GENIUS

Osler: The Man and the Legend. By W. R. Bett. (Pp. 125. 15s.) London: William Heinemann Medical Books. 1952.

It is important to be born at the right time. Most of us are born too soon or too late. Osler was born exactly at the right time for the flowering of an elusive but compelling genius. He died 33 years ago, so that there cannot be any medical men not already beyond middle life who met him in the flesh. And yet he still exerts, as he always excited, a fascination, especially upon younger medical men. With much sympathy and learning Dr. Bett seeks here to analyse this strange power of one who, being dead, yet speaks. It is not easy to explain this power, and perhaps Dr. Bett has come as near as any. The puzzle is that in so many of the things that can be listed, described, and analysed Osler comes near the highest distinction without quite reaching it. But, in fact, those who remember him will recognize that in two respects in which men are not easy to arrange in order of merit he attained as high a rank as is given to mortals : the first is in completeness of personality and the second is in completeness of sympathy. Osler was a lover, a lover of his kind, a lover of his profession, a lover of aspiring youth, and a lover of knowledge. For his loves all his faults may easily be forgiven. He was a great man, and his memory is secure. Students especially will read Dr. Bett's little book with delight.

CHARLES SINGER.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY MAY 31 1952

CORTISONE IN CARDITIS

Following the first flush of enthusiasm after the early accounts of cortisone and A.C.T.H. therapy in rheumatoid arthritis and other collagen diseases,[1] a wave of disappointment has spread through many of the more recent reports. Hench[2] himself was the first to give warning that suppression and not cure of the disease was all that could be expected. Boland[3] expressed himself in stronger terms, and, whilst acknowledging cortisone as a powerful weapon in the management of many cases, did not recommend it as the treatment of choice for most patients with rheumatoid arthritis. Its limited value in Still's disease has also been stressed.[4]

The same sort of story can be told about several other allied disorders in which dramatic remissions have been brought about by the use of cortisone, only to be followed by almost equally severe relapses when it was stopped. It would therefore indeed be remarkable if rheumatic fever were to prove the exception, but some hope of success has been reported from several sources.[5-9] Other physicians were not so impressed.[10]

On page 1145 of this issue Drs. E. N. Chamberlain, J. D. Hay, and D. M. Freeman describe their experience with cortisone in cases of acute rheumatism, including both the mildest and the most severe forms. Their results are most discouraging, and among the 11 children they studied three died during or soon after cessation of treatment. In the others there was no conclusive evidence of any modification of the carditis, although in two cases there appeared to be some reversal of the physical signs. On the other hand some improvement in the general state of health was observed even in very severe forms of the disease, and arthritis, when present, was quickly brought under control. This and the beneficial effect on what might be termed minor manifestations of the rheumatic state, such as a raised temperature, pulse, and erythrocyte sedimentation rate, has been the general experience of others, whereas nodules, a rash, and chorea[11] remain uninfluenced.

Dr. Chamberlain and his colleagues observed quite severe relapses soon after their treatment ceased. The short period—on an average 14 days—over which they decided to give cortisone was probably responsible for this. Early relapse in rheumatoid affections when therapy stops has been the common experience, but with a longer course of about six weeks this has not been a feature in acute rheumatism. A short "rebound phenomenon" is not infrequent, but in most cases the patients' own defences seem capable of overcoming this. It would therefore appear unfair conclusively to dismiss cortisone as ineffective in rheumatic carditis from a study of a series of cases on such a short course of treatment, and the authors admit this in their conclusions.

Full repair of well-established valvular lesions can hardly be expected, and the most hopeful approach is the use of cortisone or A.C.T.H. at the onset of a first attack in an attempt to prevent cardiac complications, or during a relapse of carditis to tide the patient over the most acute period.

The eventual outcome so far as the heart is concerned will obviously have to be judged from a long-term follow-up, and it is on this that the Medical Research Council is at present engaged, in conjunction with a similar American study. Only then will the medical profession be in a position to state categorically whether cortisone merely masks the symptoms of disease, obscuring the criteria by which the severity of an illness can be measured, or whether it can be counted as a new and valuable method of dealing with a disorder which is still one of the great menaces of childhood.

CHEMOTHERAPY OF TUBERCULOSIS

Whatever may be the future of *iso*nicotinic acid hydrazide and related drugs recently introduced for the treatment of tuberculosis, streptomycin must retain for some time a pre-eminent position as the only effective drug of which the action has been adequately studied. The stages through which this study has passed in this country are recapitulated in a paper by Dr. Marc Daniels and Professor A. Bradford Hill on page 1162, and this accompanies a report on the findings in a trial which was designed to decide the optimum dosage of P.A.S. when combined with streptomycin. The whole investigation, which has been planned and conducted by the Medical Research Council's Streptomycin in Tuberculosis Clinical Trials Committee and the Research Committee of the British Tuberculosis Association, has now been in progress for five years. Its conduct has generally been acclaimed as a model for clinical trials which must necessarily be conducted at a number of different

[1] Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F., *Proc. Mayo Clin.*, 1949, **24**, 181.
[2] *Proc. roy. Soc. Med.*, 1950, **43**, 769.
[3] *British Medical Journal*, 1951, **2**, 192.
[4] Schlesinger, B., *Great Ormond Street Journal*, 1951, No. 2, 81.
[5] Hench, P. S., Slocumb, C. H., *et al.*, *Proc. Mayo Clin.*, 1949, **24**, 277.
[6] —— Kendall, E. C., *et al.*, *Arch. intern. Med.*, 1950, **85**, 545.
[7] Barnes, A. R., and Smith, H. L., *Mod Conc. cardiovasc. Dis.*, 1950, **19**, 59.
[8] Keith, J. D., and Neill, C. A., *Canad. med. Ass. J.*, 1951, **64**, 193.
[9] Coste, F., *et al.*, *Bull. Soc. méd. Hôp., Paris*, 1950, **66**, 1577.
[10] Harris, T. N., *et al.*, *Circulation*, 1951, **3**, 215.
[11] Dixon, E. St. J., and Bywaters, E. G. L., *Arch. Dis. Childh.* 1952, **27**, 161.

centres. The definition of a case acceptable for treatment has been unchanged throughout: "acute progressive bilateral pulmonary tuberculosis, believed to be of recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15–30." No case has been accepted until reviewed by a central panel, and after acceptance each has been randomly allocated to a treatment group. Records have been kept on a uniform system, and *x*-ray changes assessed by an independent observer unbiased by any information about the treatment employed. Finally the whole of the results have been submitted to a masterly and searching analysis which leaves no question about their significance unanswered.

It is first made clear in the present review that the cases have been comparable from beginning to end of the whole trial: owing to this and to the fact that one treatment group has been common to each series and that preceding or following it, it is now justifiable to compare the results as a whole. They may be expressed shortly by saying that, whereas the proportion of patients improving on bed rest alone in the original series was only 33%, P.A.S. alone caused improvement in 56%, streptomycin alone in 71%, and streptomycin together with P.A.S. in nearly 90%. If "considerable improvement" be taken as the criterion, the proportion showing it on bed rest alone was only 8%, on P.A.S. alone 22%, and on streptomycin slightly over 50%, regardless of whether P.A.S. was given in addition.

Combined treatment has two objects. P.A.S. is a chemotherapeutic agent in its own right, and its effect should be at least additive to that of streptomycin; but the administration of two drugs together tends strongly to prevent the development of bacterial resistance to either, almost certainly because each blocks an alternative metabolic pathway to that blocked by the other. In the first series, including a group having combined treatment, the full daily dose of 20 g. of P.A.S. was given. Three months of this treatment is an ordeal for many patients, since this large dose is liable to cause diarrhoea or nausea and vomiting. It was therefore important to know whether a smaller dose of P.A.S. would adequately serve the same purpose. The stage in the trial now described for the first time is therefore a comparison of the effects of daily doses of 20, 10, and 5 g. of P.A.S., together with a standard daily dose of 1 g. of streptomycin continued for the usual period of three months.

The lower doses of P.A.S. had their desired effect in the lower incidence and milder character of gastro-intestinal disturbance. They also appear to have had equivalent chemotherapeutic effects. It is a notable fact that as judged either by radiographic changes or by sputum examination there is nothing to choose between the three groups. On the other hand, it is abundantly clear that the lower the dose of P.A.S. the more often does bacillary resistance develop. The percentages of patients receiving respectively 5, 10, and 20 g. of P.A.S. from whom resistant bacilli were recovered in the third month were 32, 8, and 4; and in the fourth month 47, 43, and 15, in the fifth 41, 28, and 8, and in the sixth 36, 30, and 7. The difference is even more marked, although the figures are small, if only a high degree of bacillary resistance is considered. The authors of the report define two grades, of which the "moderate" is not considered to preclude successful further treatment. It has thus been clearly proved that in order to insure as far as possible against acquired bacillary resistance the original full dose of P.A.S. must be given. It is particularly interesting that in the later stages of a six-months period of observation the effects on bacillary resistance of doses of 5 and 10 g. differ very little, whereas the difference between that of 10 and 20 g. is pronounced. It seems that the highest dose must traverse a critical level beyond which this particular effect on the metabolism of the bacillus is almost regularly exerted. Acquired resistance to P.A.S. was rare, being observed in only three cases. The data now available also enable the authors to assess the effect on prognosis of acquired bacillary resistance to streptomycin. This has hitherto been difficult, because resistance develops more often in patients more acutely ill at the start of treatment as well as in those with gross cavitation. By separating patients into groups according to clinical condition it has been possible to disentangle these factors, and it becomes clear that among comparable patients a substantially greater proportion do badly when their bacilli undergo this change.

With the publication of these reports the standard treatment for tuberculosis, at least in this form, may be said to have been defined. As the authors remark, there is only one other known way of discouraging bacillary resistance, and that is to administer streptomycin less frequently: administration twice weekly has been common American practice and is said to give as good results as one daily. A group treated in this way would have formed a valuable addition to the trial, but in an investigation so conducted treatment groups cannot be multiplied indefinitely. The present standard treatment will doubtless be that with which the latest drugs are compared, and anyone studying these reports will understand that he has inevitably some time to wait before an authoritative decision on the value of a new drug in this disease can be forthcoming.

CHARGES ON PRESCRIPTIONS

The charge of 1s. on prescriptions and certain other charges are to be made on Health Service patients from June 1.[1] There has been opposition on principle to the idea of doctors' collecting money from patients on behalf of the Treasury, but the new scheme is in one important respect more satisfactory than the previous one.[2] Dispensing doctors are made responsible for collecting the charges from their patients in cash or stamps, and the obligation is put upon them to send this money in the form of stamps to the executive council. There will thus be no deductions from their quarterly cheques as was previously envisaged, and the General Medical Services Committee and its chairman, Dr. Wand, are to be congratulated on so forcibly resisting the original scheme that the Government has conceded a more acceptable alternative. The charge is one about which the Government has been adamant. The cost of prescribing and the number of prescriptions have risen every year since the Health Service started, and the Government sees in these charges a way of increasing revenue, of reducing the pressure on doctors, and, what is more important, of discouraging the bottle-of-medicine habit.

The obligation put on the dispensing doctor is to obtain from his patient a shilling either in cash or in stamps when he supplies medicines or dressings "on one occasion." This phrase means in effect one treatment between two attendances or visits and may cover a number of separately prescribed items. But a repeat supply is not deemed to have been given on the same occasion. The patient is not himself obliged to buy stamps, though it is hoped that most will. If a patient insists on paying cash the doctor, who will probably find it most convenient to have available a block of stamps, will stick one of them on a special card in the presence of the patient. The patient will thus be left in no doubt that his shilling is a tax paid to the Treasury. At the end of the month the doctor sends the stamps to the executive council for crediting to public funds, and that is why deductions from his remuneration are not necessary. This is bound to be an irksome procedure, and it is to be hoped that the Ministry of Health will not neglect to inform the public fully of how they are to make these payments and what their purpose and destination are. The rural patients under the scheme are not being treated any more advantageously than those in towns.

Local medical committees are to be given powers to review cases in which the doctor seems to be sending in too few stamps. In other words, if an executive council finds that a doctor is sending in too few stamps in relation to the number of patients on his dispensing list in comparison with other dispensing doctors in his area the local medical committee will ask for an explanation. It is to be expected that discussion with the doctor concerned will suffice here, though disciplinary powers of some kind are to be conferred on local medical committees. The non-dispensing majority of general practitioners will continue to write prescriptions as at present, and their patients will pay their 1s. to the chemists, whose remuneration is to be adjusted accordingly, though in rural areas arrangements like those for dispensing doctors may be made for them.

On the whole the scheme is a compromise between the Government's resolution to levy the tax and the doctors' reluctance to collect it. Certain classes of patients can claim refund of payment—specifically, those in receipt of national assistance, others not receiving national assistance but who can show that payment would cause hardship, and those pensioners whose treatment is for a war disability. There is a good case here for seeing whether these categories should be extended to include, for example, old-age pensioners.

[1] See *Supplement*, p. 276.
[2] *Supplement*, February 9, p. 47.

PRESIDENT, 1953–4

The Council has recommended to the Representative Body that Mr. J. W. Tudor Thomas, M.S., F.R.C.S., be appointed President of the British Medical Association for 1953–4. A distinguished ophthalmic surgeon with an international reputation, Mr. Tudor Thomas has made original and lasting contributions, both experimental and clinical, to the technique of corneal transplantation. Before the last war he first conceived the idea of a registration bureau for the collection and use of donor material at the Central London Ophthalmic Hospital. Eye banks were subsequently formed at East Grinstead and in the U.S.A., and the latest development is a Parliamentary Bill, now in its final stages, providing for the use of deceased persons' eyes for corneal grafting. Mr. Tudor Thomas holds among his many appointments that of ophthalmic surgeon to Cardiff Royal Infirmary and lecturer in ophthalmology to the Welsh National School of Medicine, and he has also found time to give abundant service to the profession through the B.M.A. A member of Council for the last three years, he has served on many of its committees and on the Representative Body; in 1947–8 he was chairman of the Cardiff Division.

DEATH ON THE TABLE

The heart may stop suddenly in the operating theatre from the effects of anoxia or of drugs used by the surgeon or anaesthetist—an overdose of local analgesic or of chloroform most frequently, less commonly of trichlorethylene, intravenous barbiturates, adrenaline, or prostigmin. In thoracic surgery the cause may be manipulation of the heart or hilar structures, or coronary ischaemia due to pressure. Pulmonary embolism may occur on the operating-table, or the patient may suffer a coronary thrombosis during a period of hypotension, as produced by spinal analgesia. Cardiac massage is usually performed in every case: but, in the flurry, is it done effectively or, indeed, with any result at all?

Cardiac massage should be started at once, and time not wasted with the injection of stimulants. The most effective way of performing it is indicated by the animal

experiments of Drs. J. Johnson and C. K. Kirby,[1] of the University of Pennsylvania. They recommend that the human heart should be compressed 120 times a minute, preferably between two hands; this rate rapidly tires the operator, and an assistant should be ready to relieve him. The highest rates of blood flow produced by manual contraction of the dog's heart could not be maintained unless blood or saline were given intravenously, and they emphasize that intravenous fluids should not be neglected in the excitement inseparable from the performance of cardiac massage in the operating-theatre. They believe that massage through the diaphragm is not effective, and they dismiss the supposition that artificial respiration can itself result in significant circulation. Whatever form of massage was used, in their experiments the rate of blood flow never rose above half that produced by the spontaneous heart-beat in the open chest.

In an attempt to make cardiac massage more effective Johnson and Kirby tried compression of the root of the aorta distal to the origin of the subclavian artery, a manœuvre introduced by J. C. Wiggers,[2] and found this greatly improved the cerebral and coronary blood flow. The use of aortic occlusion in a human being has now been reported by M. G. Carter,[3] of Boston City Hospital. His patient was undergoing thoracotomy for an extensive carcinoma in the left lower lobe bronchus, under gas, oxygen, and ether anaesthesia administered by endotracheal tube. There was a large amount of secretion, which demanded frequent tracheal suction—a procedure proved to cause anoxia—and after a particularly vigorous aspiration the heart stopped. As the chest was already open cardiac massage was started immediately at a rate of 60 contractions a minute, while the anaesthetist gave artificial respiration with oxygen under pressure. There was no detectable blood pressure until the operator compressed the aorta distal to the origin of the left subclavian artery with his hand; a systolic pressure of 60 mm. Hg was then measured, and the pulse was perceptible at both wrists. Massage was maintained at the same rate by the surgeon and his assistant, who worked for periods of five minutes each, and after 25 minutes the heart began its normal rhythm. The patient had an uneventful postoperative course and showed no mental deterioration.

The thoracic surgeon has the advantage that the heart and great vessels are usually exposed, and he may usefully try compression of the aorta in the way described by Carter. Whenever cardiac massage is carried out through an abdominal incision it would seem wise for the surgeon not to attempt it through the intact diaphragm. Two operators alternating with each other should squeeze the heart at a rate above 60 a minute, and artificial respiration with oxygen under pressure must be given at the same time. Adrenaline may be injected into the myocardium to augment the stimulus of massage, but the surgeons' fingers must maintain an adequate circulation in the cerebral and coronary vessels as long as there is any possibility of the heart restarting.

[1] *Surgery*, 1949, **26**, 472.
[2] *Amer. Heart J.*, 1940, **20**, 413.
[3] *J. Amer. med. Ass.*, 1951, **147**, 1347.

SCIENCE IN PICCADILLY

There was a large and distinguished gathering at the Royal Society's Conversazione last week. It was the annual evening party, at which interesting experiments from the year's scientific discoveries are shown to the assembled Fellows and their scientific guests, and the President, Dr. E. D. Adrian, O.M., and his wife stood in the Council Room beside the Society's Mace and Charter Book to welcome everybody in. There were 30 different exhibits, which is a full evening's work for anyone who wants to understand them all and to question all the demonstrators. Maps showed the distribution of blood groups among different populations round the world, the recently discovered manuscript of the book on astronomy written in 1392 by Geoffrey Chaucer was on view together with ultraviolet photographs to reveal the words he had rubbed out, and synthetic sapphires and rubies were being made in an automatic furnace. The smallest mammal in the world, the pygmy mouse of Africa, which is about the size of the terminal phalanx of the thumb, ran about in a cage next to its big second cousins the mole rats, one species of which is completely fur-less and was trying rather hopelessly to bury itself in some sand. As usual there was a fine display of sea creatures in bowls—crabs and shrimps and fantastic feathery worms, including one which glowed in the dark. Some tiny black staphylinid beetles were continually being thrown into a dish of water to show off their powers of high-speed surface skimming back to land. They are jet-propelled by a secretion from their anal glands, which lowers the water's surface tension locally like a piece of camphor and produces a backward water flow.

But the most remarkable biological item was the discovery of an electric sense, a kind of radar, in fish of two quite unrelated families from the rivers of Africa and South America. In their tails are weak electric organs which emit continuous electrical pulses, in some species constant at a frequency of 300 per second, in others slower but getting fast when the fish is excited. In one experiment the discharge from a male was picked up and transmitted into another tank with a second male, who at once attacked the transmitting electrodes. They have sense organs for detecting these discharges from one another and for appreciating the way rocks and earth banks distort the electric field in which they move. This enables them to swim "blind" through muddy water, or back down narrow tortuous channels without touching anything.

Two new kinds of microscope were displayed. One was the already famous flying-spot microscope—or television microscope, as the President called it—which can do a blood count by itself in 1/50th of a second. Its principle is simple. The light used comes from a cathode-ray tube, in which a sharp electron beam is caused to sweep regularly back and forth across the face of the tube so as to make it glow brightly just like the screen of a television set. In 1/50th of a second the beam has started from the top left-hand corner, traced out 405 horizontal lines one below the other to the bottom of the screen, and shot back to the start again. The grid of light passes into an ordinary micro-

scope through the eyepiece and out through the objective to the specimen. The microscope thus works in reverse, reducing the light grid to microscopic dimensions, so that the field of view is scanned completely by 405 sweeps of the beam once in every 1/50th second. Beneath the specimen is a photoelectric cell which picks up the rapid sequence of light and shadow, as the light beam is transmitted more or less completely by the specimen, and passes it to a counter and to one or more television screens on which the whole image is rapidly and synchronously built up again, with a magnification of 25,000 or even 250,000 times. The contrast can be varied by turning a knob, as in a television set, which is a great advantage when the specimen itself does not show much contrast, and a change to coloured light or to the ultraviolet is possible simply by inserting an appropriate filter. The whole instrument costs between £200 and £300.

The other microscope uses *x* rays, which are brought to a very fine-point focus, only 1/1,000 mm. in diameter, very close to the specimen, so that an enlarged shadow image is thrown on a distant photographic plate, giving a resolution and magnification like that of the conventional light microscope. Stereoscopic radiographs are easily taken, so that, for example, the microscopic anatomy of a thick slice of kidney can be displayed three-dimensionally, once it has been freeze-dried. Special stains will have to be developed for this new form of microscopy for light-opaque objects.

CONTRACEPTIVES BY MOUTH?

There was some talk at last year's International Congress of Chemistry in New York of an effective oral contraceptive said to have been under development, but few details of its mode of action were available. A recent note in *Science*[1] has summarized progress so far and reported that phosphorylated hesperidin given regularly by mouth to 30 female rats prevented pregnancy in 80% of them. It did not interfere with their oestrous cycles, since vaginal smears showed only normal changes, and most of them became pregnant soon after the administration of the drug ceased. Hesperidin is a component of vitamin P, found in various fruits and supposed to play some part in man in preventing capillary fragility. Neither it nor its phosphorylated derivative are toxic, but the latter was found in the course of experiments for another purpose[2] to be a strong inhibitor of the enzyme hyaluronidase. Several other phosphorylated or sulphonated compounds, including "suramin," once used in trypanosomiasis, also proved effective inhibitors in these laboratory tests. Now it has been known for some time that the unfertilized ovum in the Fallopian tube is surrounded by follicular cells bound together by a gel of hyaluronic acid, which must be broken down by the enzyme hyaluronidase present in semen before a sperm can penetrate and effect fertilization. Inhibitors of the enzyme should therefore be contraceptives. One type of inhibitor is the modified substrate, and nitrated hyaluronic acid placed intravaginally in rabbits prevented conception after mating,[3] though it would probably be too toxic for systemic use. Only more work with larger numbers of experimental animals and with other related compounds will show whether this promising attack can lead to an ideally suitable contraceptive.

[1] Martin, G. J., and Beiler, J. M., *Science*, 1952, **115**, 402.
[2] *J. biol. Chem.*, 1948, **174**, 31.
[3] Pincus, G., Pirie, N. W., and Chang, M. C., *Arch. Biochem.*, 1948, **19**, 388.

MOTOR-CYCLE ACCIDENTS

Motor-cycling has long been a serious hazard to young men. In 1949 in England and Wales 10% of all deaths of men aged 20–24 were due to motor-cycle accidents. The percentage was much lower in other age groups, though the next highest was 5% in the age group 15–19. To consider the problem of these accidents and to advise on measures for their prevention was the task set a Ministry of Transport Committee on Road Safety, whose report has now been published.

It begins by pointing out that, in 1951, 42,680 motor-cyclists and motor-cycle passengers were killed or injured. In September of that year the number of motor-cycles licensed was 822,571, so that perhaps one in twenty of them were involved in accidents that year. Analysing the causes of motor-cycle accidents in 1950, when there were 37,390, the report gives the opinion of the police that skidding accounted for 15%; misjudging clearance, distance, or speed 12%; excessive speed in the prevailing conditions 11%; overtaking improperly 11%; lack of care at road junctions 8%; and inattention or attention diverted 7%.

The report then goes on to discuss the influence of such dangers as bad road surfaces, stray dogs, various safety devices, and speed. While stating that speed is "a factor in the majority of road accidents" and that "speed in the wrong places and in the wrong conditions is often lethal," the committee seems not to have attached the importance to excessive speed that it might have done, for the police statistics do not bring out clearly the danger of driving too fast in relation to prevailing conditions. While 11% of the accidents are specifically attributed to this cause, it undoubtedly prevails in many accidents included in other categories. It is true that, as the report says, "bad road surfaces are a particularly serious hazard for motor-cyclists," but they are so only when the motor-cyclist is travelling too fast, for there is practically no surface that cannot be safely traversed if the motor-cyclist takes it at the proper speed. Again, "lack of care at road junctions" often means shooting over them, and "misjudging clearance, distance, or speed" often means being unable to pull up in time. Though not the subject of a specific recommendation, one important observation is embedded in the report. It is that certain makes of motor-cycle are involved in a disproportionate number of accidents, and "it seems likely that some makes . . . are less stable than others." This is well known to anyone who has ridden motor-cycles made by a number of different firms. Unfortunately the committee was too timid to say which these makes are, yet it is of great importance that the public should know and that manufacturers should not be allowed to sell machines that are more dangerous than they need be.

While the committee's recommendations are perfectly sound, they are perhaps inevitably rather disappointing. Among safety devices advocated for motor-cyclists are

crash helmets and goggles with side panels, and foot rests for pillion passengers. The committee recommends that the value of leg-guards should be investigated and that manufacturers should consider further standardization of controls. Rear-lighting of other motor vehicles should be improved and proper driving mirrors fitted. Driving tests for motor-cyclists should be conducted by examiners riding motor-cycles instead of remaining stationary as at present, and the importance of proper training is emphasized.

The committee does not recommend the imposition of any special speed limit, though a member representing the Pedestrians' Association records a reservation in favour of a 40-m.p.h. limit for riders under 21 and 50 m.p.h. for others. When vehicles which are subject to speed limits are to be seen any day on the roads exceeding it, the committee was probably right not to recommend a restriction that almost certainly could not be enforced. But it might well have recommended that much greater publicity should be given to the dangers of speeding. Even though it is expensive, a large and continuing publicity campaign—so successful in helping to combat diphtheria and venereal disease—might have some success in reducing the 40,000-odd injuries and deaths that occur yearly. The problem of motor-cycle accidents is part of the much wider problem of road accidents, as the report concludes. It is unlikely to be tackled seriously until the nation feels much greater dismay than it does now at the daily destruction of life and limb on the roads.

GREAT ORMOND STREET CENTENARY

The centenary of the Hospital for Sick Children, Great Ormond Street, was commemorated on May 27 by a Thanksgiving Service at St. Martin-in-the-Fields, followed by the laying of a stone by H.R.H. the Princess Royal on the site of the new out-patient department and the unveiling of a statue in memory of Viscount Southwood, chairman of the hospital from 1939 to 1946. It was in 1852 that the lease of a seventeenth-century house in Great Ormond Street—a house which had belonged to Dr. Mead, physician to Queen Anne—was bought by Dr. Charles West and converted into a children's hospital. The present fine block was opened by King George VI and Queen Elizabeth in 1938.

The celebrations of the centenary were preceded by a clinical meeting on May 26, when a series of demonstrations were given by members of the staff in the theatres, the medical and surgical wards, the virus laboratory, and the departments of clinical pathology, morbid anatomy, biochemistry, radiology, and medical illustration. In the department of psychological medicine a demonstration of intelligence testing was given, and in the museum a number of historical specimens were on view.

On Tuesday afternoon the hospital put on its best clothes to welcome the Princess Royal, who is its patron. She was received by Sir William Douglas, chairman of the Board of Governors, and made her way through a guard of honour of nurses to the dais, where a bouquet was presented. Then, at the south entrance, she unveiled the fine statue of St. Nicholas (by Mr. Gilbert Ledward, R.A.) in commemoration of Lord Southwood. The statue will form part of the Great Ormond Street entrance gate. Returning to the dais, the Princess Royal then laid the commemorative stone on the site of the new out-patient department, the long-planned work on which begins this year.

Sir William Douglas read a number of congratulatory telegrams, including one from Baltimore, from Sir Allen Daley, a member of the board, and another from the Hospital for Sick Children, Toronto. He mentioned some of the benefactors of the hospital during the last hundred years. "During the next hundred years we shall have a still more marvellous hospital and more marvellous techniques, but I am bound to say that they will never excel us in their devotion to the sick children."

The Princess Royal said that the hospital had a special place in her affections. Her personal association with the hospital went back to the time of the first world war, when she put on uniform without quite knowing what lay before her. The fact that she was privileged to serve in a ward here, even in quite a humble capacity, had given her great pleasure and happiness. In touching on the history of the hospital, she spoke in particular of Lord Southwood and, belonging to an earlier day, of Charles West, the founder.

Mr. James Crooks, F.R.C.S., chairman of the Medical Committee, in thanking her Royal Highness, said that all those who had worked in the hospital had a lifelong affection for it and believed there was no other place like it. They were now going to have a building which would be worthy of the children of Britain, who came from all parts of the country to that hospital.

The large company attending the ceremony included the Bishop of Stepney, and the Mayors of St. Pancras and Holborn. The event coincided with the publication of a history of the hospital, *Great Ormond Street, 1852–1952*, by Mr. T. Twistington Higgins, senior surgeon to the hospital, who contributed an article on its centenary in the *Journal* of February 16.

THE STEWART PRIZE

Every two years the British Medical Association awards the Stewart Prize in recognition of important work done on the origin and spread of epidemic disease. At the meeting of Council on May 21 Sir Henry Cohen, immediate past President and acting President of the B.M.A., presented the Stewart Prize to Dr. C. H. Andrewes, F.R.S., F.R.C.P., who, as Sir Henry said, "has not merely extended our knowledge of the natural history of virus infection, but (he) has endeavoured to overcome virus infection by paying considerable attention both to prevention and cure." Dr. Andrewes, one of the discoverers of the influenza virus, is a member of the scientific staff of the National Institute for Medical Research, director of the World Influenza Centre in London, and is in charge of the scientific work at the Common Cold Research Unit at the Harvard Hospital, Salisbury. There could be no more suitable recipient for the Stewart Prize, for readers of this and other journals well know that Dr. Andrewes's contributions to medical science are readable, instructive, and entertaining—a rare combination.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

RHEUMATOID ARTHRITIS

BY

W. S. C. COPEMAN, M.D., F.R.C.P.

Physician-in-charge, Rheumatism Department, West London Hospital

Rheumatoid arthritis is a general disease of unknown aetiology which is characterized clinically by a condition of non-suppurative polyarthritis. Pathologically the basic lesion is one of fibrinoid degeneration of the collagen component of the fibrous tissues. It is therefore an important member of what is often termed the collagen group of diseases.

Rheumatoid arthritis has been known under many names, which include atrophic arthritis, proliferative arthritis, arthritis deformans, and infective polyarthritis. When it occurs in children it is known as Still's disease. The disease may start at any age, but in the recent survey made by the Empire Rheumatism Council the age at onset in 532 patients was 41.5 years. Females are affected at least three times as frequently as males, and this preponderance is greater in the lower age groups. It was also established in the course of this survey that there is some familial tendency to develop the disease. It is thought that about 4% of the female population of this country are victims, and that the cost to the country is about one million pounds annually.

Aetiology

Although the aetiology of this disease is unknown, there are a number of factors which are far-reaching in their effects as predisposing or precipitating agents in certain patients. Amongst the intrinsic factors of this nature may be mentioned the patient's body-build (somatotype), abnormalities of the peripheral circulation, endocrine factors, metabolic and nutritional disorders, and response to stress. Of extrinsic factors such traditional entities as climate and environment, infection, and psychological upset or shock may be mentioned; while both pregnancy and jaundice will produce remissions of the established disease. In most cases the disease appears to result from the interplay of such factors, although future research may disclose some single aetiological factor.

Pathology

The pathological process as seen in the synovial membrane of the affected joints is inflammatory in nature. Later this spreads to the capsular, tendinous, and subchondral tissues, and the cartilage is invaded from beneath. Fibrous tissue later replaces these structures, and ankylosis will occur owing to the fusion of the layers of fibrous tissue on opposing joint surfaces. If untreated the affected joints will generally become immobilized in the position of flexion as the result of spasm of the surrounding muscles. The earliest radiographic appearance is osteoporosis of the bone ends. Later, marginal erosions and diminution in the affected joint spaces will be seen, and small cystic areas of degeneration are not unusual. In the latest stages joint disorganization and even bony ankylosis may occur.

In the active stage of rheumatoid arthritis the erythrocyte sedimentation rate is always raised, and progress can be followed by routine repetition of this simple test. Some degree of anaemia of the hypochromic type is also commonly found, and this generally fails to respond satisfactorily to the oral administration of iron. The serological tests formerly used to indicate the presence and degree of activity of the haemolytic streptococcus are not nowadays used. The albumin/globulin ratio in the plasma is generally reversed in active cases, although the total protein content may be normal.

Clinical Features

A period of general ill-health which may be characterized by undue fatigue, pallor, loss of weight, paraesthesiae of the limbs, tachycardia, and muscular stiffness often precedes the onset of the articular phase of the disease. This may give rise to considerable diagnostic difficulty and uncertainty. When the condition starts acutely with pyrexia the clinical picture may resemble that of an infection, while in those cases in which the arthritis is of a fleeting nature the diagnosis of rheumatic fever may be suggested. Certain cases remain non-articular for weeks or even months, and tuberculous infection or trauma may then appear likely causes. In view of the great variation possible in the type of onset the following conditions, in addition to those already mentioned, may have to be distinguished from rheumatoid arthritis: gonococcal and acute suppurative arthritis, Reiter's syndrome, gout, osteoarthritis, disseminated lupus erythematosus, syphilitic arthritis, scleroderma and dermatomyositis, polyarteritis nodosa, and the joint symptoms of purpura or haemophilia.

In a classical case the small joints of the hands and feet will rapidly become swollen and painful, and the process will then progressively involve the larger joints, and sometimes even the spinal column and jaws, although remissions and exacerbations are to be expected at this stage. Morning stiffness is a prominent symptom, the patient often being almost helpless early in the morning, but regaining considerable freedom of movement later in the day. Persistent attempts on the part of the patient to "walk it off" will generally result in an increase in joint effusion, muscle spasm, and, later, flexion deformity and permanent impairment of function.

Muscle wasting is often a prominent feature of these cases, and in the hands this may result in ulnar deviation and subluxation of the metacarpo-phalangeal joints. Abduction and rotation of the shoulders is generally much restricted, particularly in patients who are confined to their bed or a chair. Flexion of the knees as the result of powerful spasm of the hamstring muscles will generally occur in cases inadequately treated, and constitutes a serious and disabling deformity. Even when the active phase of the disease subsides, pain and disability are likely to persist in such cases as the result of residual joint damage. In the later stages of the disease, in addition to permanent deformity of the joints, there may be profound emaciation and anaemia, and the patient may die of intercurrent infection. Psoriasis is not infrequently associated with rheumatoid arthritis, and the association of these conditions is thought by some authorities to increase the gravity of the prognosis.

Prognosis

It is a matter of the greatest difficulty to forecast the course that the disease will run in any particular patient. The type of onset gives no clue to its subsequent behaviour. The average case runs a course in which exacerbations and remissions may alternate over many years. It is thought that if a group of average well-treated patients were followed over a period of ten years, at the end of that time 45% would be stationary, 50% would be in remission or improved

to some extent, while the rest would be crippled in varying degrees. As Davidson has said, "The attitude of the physician should be one of cheerful optimism, as in about half his patients this will be justified by results, and in the other half much can be done to conserve function and prevent deformity."

General Management

There is no specific curative agent known which is uniformly effective in the treatment of rheumatoid arthritis. The application of more scientific and critical methods of assessment in the past few years has destroyed the claims made on behalf of a number of remedies previously believed to be effective. Nothing will be lost by the patient being aware of this, since the hope of a magical cure will militate against acceptance of methods of treatment which may require life-long application and co-operation. In many cases the patient must be taught and helped to "live with his disease." The enlightened application of methods of treatment aimed at maintaining or restoring a reasonable level of function, together with the relief of symptoms, notably pain, will retain the patient's active co-operation and produce improvement or remission in at least half our patients.

In the early stages, when constitutional symptoms are severe and the affected joints are swollen and painful, there should be no alternative to rest in bed. It is at this stage, and not at the stage of crippledom, that such patients can most profitably be admitted to hospital. During this period the affected joints should be immobilized for most of the time by means of plaster-of-Paris splints, which can easily be moulded to the limbs. The physical condition of the body will, however, deteriorate if the rest is too complete, and if this occurs subsequent rehabilitation may be retarded. A compromise must therefore be adopted whereby the benefit of this rest is combined with the performance of general bodily exercises which are designed to maintain the functional integrity of the main muscle groups in the gluteal, lumbar, and thoracic regions, as well as those controlling the limbs. These exercises are known to all well-trained physiotherapists.

The position of the patient in bed must also be regulated so that the spine is not maintained in a position of flexion, with consequent restriction of thoracic movement. The knees must not be helped into contraction by allowing a supporting pillow, and the feet must not be allowed to drop as the result of pressure by the bedclothes. The bad reputation of rest in bed in this disease arose purely as the result of failure to recognize the importance of these simple, but fundamental, principles. In addition, such factors as a nourishing mixed diet, good nursing, and cheerful surroundings will help to forward the physical and mental regeneration of the patient.

Most patients suffering from this disease are underweight, and in such cases it is important to secure an adequate intake of protein, together with an ample supply of vitamins and minerals, such as are indicated in all patients who are suffering from a chronic wasting disease. Extra fat is also indicated in the form of milk, cream, eggs, and butter.

Relief of Pain, Sleeplessness, and Anaemia

It is important to prescribe both hypnotics and analgesics in adequate regular dosage during the acute phase of the disease, since lack of sleep and the endurance of needless pain will produce very rapid deterioration in the patient's condition. Aspirin in one of its forms is the most readily acceptable analgesic in doses of 10 to 15 gr. (0.65 to 1 g.) every four hours. This can be alternated with tab. codein. co. (*B.P.*), two tablets after each meal. As a hypnotic, in cases in which sleep is disturbed, this may be reinforced with one of the barbiturate preparations, taken with a hot drink last thing at night.

A common feature of rheumatoid arthritis is anaemia, and iron should therefore be administered as a routine in the form of the ferrous salt. If this proves ineffective the intravenous route should be substituted for the oral. A reliable preparation can be injected twice a week on four or five occasions with advantage. Toxic symptoms practically never result from this procedure, but the subjective improvement manifested by the patient as the blood improves is often rapid and considerable. Blood transfusion, on one or more occasions, is also a useful supporting measure and probably merits more frequent use in this disease.

Gold

It is generally recognized, although it has not been scientifically proved, that the employment of gold salts by intramuscular injection will have a beneficial effect upon the course of active rheumatoid arthritis in most cases. It is also generally believed that the maximum therapeutic response to gold is likely to occur during or following the first course of injections, although this is not invariably so. The toxic reactions which may follow the injection of gold salts have probably received more than their fair share of publicity, since they are serious enough to cause treatment to be withheld in only 4 to 5% of cases. Toxic reactions include irritation of the skin, which may be followed by an erythema or a morbilliform rash, and if treatment is not stopped this may progress to the stage of severe exfoliative dermatitis, which will necessitate special treatment with dimercaprol. Such patients should never receive gold again. Less serious complications of this method of treatment are stomatitis, transient albuminuria, and very occasionally a toxic nephritis or hepatitis. Agranulocytosis has been reported on one or two occasions.

Gold should never be the only form of treatment used, since it will do nothing to prevent deformity; nor should it be used as a last resort in a severely crippled patient. Its only function is to lessen the activity of the unknown disease-process in the blood stream.

There are several preparations of gold salts on the market. Preference should be given to the water-soluble salts which are given by intramuscular injection. Colloidal preparations are believed to be less effective. Injections are generally given at intervals of a week. The first two or three should be very small (0.01 g.), in order to test the patient's sensitivity. If no contraindication has arisen this dosage can then be doubled, and after a further few injections raised to 0.05 g. and continued at this level until a total of 0.5–1 g. has been administered. If improvement occurs after or during this course of treatment a further similar course may be embarked upon after an interval of four to six months, or at the first sign of renewed activity of the disease. Some authorities prefer the alternative of a fortnightly maintenance dose of 0.05 g. for a few weeks after the termination of the complete course, after which the time interval can be lengthened to once a month, and maintained in this way for six to twelve months.

It is important to question the patient for early signs of toxicity at each visit, otherwise such early toxic signs as a metallic taste, itching of the skin, or purpuric spots might be ignored. It is wise also to examine the urine for albumin on each occasion, and an occasional blood count should be made during a long course of treatment. Should any abnormality be noticed gold should be stopped until it has disappeared. Gold is contraindicated in old patients or in cases in which there is evidence of disease of the kidneys, liver, or bone marrow, and also in cases of severe skin disease other than psoriasis.

Other Remedies

Copper salts have recently been introduced as an alternative to gold in cases in which the latter for any reason is not well tolerated. Experience of them in this country does not seem to have been encouraging, however. Bismuth has also been recommended for the same reason, but no appreciable benefit is generally observed as the result of its use.

Claims have been made in the past for numerous remedies for rheumatoid arthritis. These are too numerous to mention in detail, but it can be said with some confidence that few, if any, of these if subjected to controlled clinical assessment could be shown to have more than a placebo value. The list would include such diverse entities as iodine lockets, bee venom, vitamin D in enormous dosage, cobra venom, guaiacol, chaulmoogra oil, sulphur (both internally or sprinkled in one's shoes), and celery salt with every meal.

Focal Infection

The belief that rheumatoid arthritis is caused by obscure focal infection is no longer widely held in this country or America. The removal of teeth and tonsils or the surgical approach to nasal sinuses on suspicion alone is therefore not generally encouraged. Obvious infection in any site should naturally be approached in a rational spirit owing to its secondary deleterious effect on chronic disease of this type. Vaccines are not now often thought to be indicated in the treatment of rheumatoid arthritis in which no specific infection can be demonstrated.

Care of the Joints

In cases in which muscle spasm is pulling the joints into a position of flexion a plaster-of-Paris splint should be applied, so as to immobilize them in their best position for a few days. Spasm and pain will be abolished by this procedure, and after a few days the splint can be removed and the joint put gently through full movement in order to prevent adhesions forming. Another plaster can then be applied, and it will generally be found that on this second occasion it will be possible to fix the joint in full extension. After a week this also should be removed and the posterior portion retained for use as a gutter splint. The affected limb should be bandaged into this for most of the day, being removed only for gentle movement once daily.

Later, further measures will be required to restore active function and stability of the affected joints: these will involve the re-education of the muscles which should control these joints. Premature weight-bearing in the absence of such control must be avoided, since it will lead only to a recurrence of pain and effusion, and so to further muscle-wasting. This stage of muscle re-education consists in skilfully graduated resisted exercises and physiotherapy, which may lead on to the use of the stationary bicycle or rowing machine before actual walking is allowed with or without the help of crutches or sticks. It is important that the patient shall understand that full restoration of function ultimately depends upon his own efforts, which are supplemented, controlled, and directed by the doctor and the physiotherapist in consultation. Pain can be relieved with the help of heat in various forms, which may vary according to circumstances from poultices to short-wave diathermy, but massage is seldom indicated in active rheumatoid arthritis.

In the later stages of rehabilitation purposeful activity in the form of occupational therapy may supersede routine exercises in re-educating the patient in the use of his limbs and in restoring manual skill and dexterity. It will also restore the power of concentration, which often tends to be lost as the result of chronic illness.

In patients who become severely crippled in spite of adequate medical treatment certain orthopaedic measures may become necessary, and skilled surgical intervention if necessary need no longer be delayed on account of the disease being in an active stage.

Cortisone and A.C.T.H.

Three years ago Hench and his colleagues announced that they had been able to suppress the symptoms of rheumatoid arthritis by the administration of Kendall's compound E—now called cortisone—and of A.C.T.H. (adrenocorticotropic hormone). This claim has subsequently been amply confirmed. It is important to realize, however, that it is *suppression* and not *cure* of the disease which is achieved by the use of these hormones, and thus relapse is usual soon after their administration is stopped. They are difficult to procure and expensive, and their prolonged use, which is necessary in a chronic disease such as rheumatoid arthritis, is apt to produce undesirable side-effects. Until these disadvantages have been overcome the use of cortisone and A.C.T.H. cannot be recommended as a routine procedure in a busy general practice, as much time and trouble are demanded by their successful use.

Their clinical suppressive effect is remarkable, and improvement generally occurs in the following sequence. First, stiffness is relieved, and then pain, tenderness, and swelling of the affected joints. Fever, if present, disappears, and the patient's appetite and weight increase. All this is accompanied by a sense of well-being which will often amount to euphoria. Cases in which the joint changes are potentially reversible will become practically symptom-free in seven to ten days, although some will continue to manifest minor signs of activity of the disease. The E.S.R. falls and the anaemia tends to revert to normal, as do the plasma proteins.

The dosage of cortisone originally recommended was 300 mg. on the first day, 200 mg. on the second day, and subsequently 100 mg. daily. Recent workers tend to adopt a lower scale and endeavour to maintain the patient on the lowest possible dosage consistent with reasonable comfort, since in this way the risk of side-effects is lessened. Some patients can be maintained on a daily dosage as low as 50 mg. or less with reasonable efficiency. Cortisone can be given either by injection or, in slightly higher dosage, by mouth. A.C.T.H. has to be given by injection every six hours; 40 mg. of A.C.T.H. is roughly equivalent to 100 mg. of cortisone.

The chief side-effects produced by these hormones are the result of their excessive physiological action, and consist principally in sodium retention (oedema), potassium excretion (muscle weakness), excess of sex-hormone production (acne, hirsutism, etc.), abnormalities of carbohydrate metabolism (diabetes), and cerebral stimulation (psychosis). Hyperadrenalism in the form of Cushing's syndrome may also occur. Other somewhat less important side-effects will include pigmentation, alteration in the facies, striae, rise in the blood pressure, tachycardia, and irregularity of the monthly periods. Wound healing may also be delayed, and the symptoms of the onset of acute inflammatory disease such as appendicitis may be masked. The chief contra-indications to the use of cortisone and A.C.T.H. are incipient heart failure from any cause, thrombosis, diabetes, hyperpiesis, renal or tuberculous disease, and an unstable personality.

The mode of action of these hormones is completely unknown. With further experience of their use, together with technical improvements, which should result in a prolongation of their action and the elimination of side-effects, they will take their place as a very valuable medical treatment in selected cases. It is unlikely, however, that their use will ever entirely eliminate the need for the use of the other less specific types of treatment which have been briefly described above.

Next Refresher Course Article.—"Fractures in the Aged," by Mr. Richard H. Metcalfe.

The International Hospital Federation has chosen the week immediately preceding the Coronation for the Eighth International Hospital Congress—the first to be held in Great Britain. It will take place in London from May 25 to 30, 1953, and 1,000 delegates from some 30 countries are expected to attend. The meetings will be held at Church House, Westminster, where the Houses of Parliament met during the war years. A Hospitals Exhibition will be held in conjunction with the congress.

Nova et Vetera

THE UNTIMELY BIRTH OF A CHEMICAL DISCOVERY

The Essays of Jean Rey. A facsimile reprint of the original edition of 1630, with an introduction by Douglas McKie, D.Sc., Ph.D. (Pp. 144; 21s.) London: Edward Arnold and Co. 1951.

In our first lesson in chemistry we learnt that matter, in the chemical sense, is uncreatable and indestructible. Therefore, we were told, if the amount of matter (as determined by weight) be reduced in any chemical process, it is the chemist's business to find where it has gone. Of course this simple view did not begin with the rise of science, for, in a rough sense, it has always been known. If the housewife stored two pounds of flour in her cupboard and found only one pound on going to it again, she made it her business to find who had taken it; she did this when the Pyramids were built just as she does to-day. Nevertheless the rule was not recognized as quite universal. After all, there was such a thing as magic. Moreover, for the 1,500 years that the alchemists were at work, the principle of indestructibility and uncreatability of matter was allowed to have some exceptions.

We can see now that one basis of fallacy among the alchemists was that "air"—which included for them all gaseous material—has no weight. In those days and among such people the nature of combustion was a special puzzle. In ordinary burning, as of wood or coal, weight is obviously lost. It was assumed that the same was also the case with combustion—that is, calcination—of metals. Thus it was that chemistry became bedevilled by the doctrine of *phlogiston*, formally introduced in 1669 by the German mining expert, J. J. Becher, but tacitly implied for centuries before his time. Phlogiston was a hypothetical substance which left bodies, metals like others, in the process of burning. Thus the calx of a metal should weigh less than the metal. For a century phlogiston was a normal term of chemistry, from whence it was exorcized by Lavoisier in 1777. Dr. McKie is the recognized authority on Lavoisier and his work. He is thus exactly the right man to edit a book that in some degree forestalled Lavoisier by more than a century. It is astonishing that the evidence on which Lavoisier based his view of calcination had been available for all that time, had Lavoisier but known it. Dr. McKie has rendered a great service to the history of science by making this remarkable document accessible to the modern reader and for presenting it in his usual clear and attractive manner. It gives a good picture of a rational alchemist at work.

The *Essays* of Jean Rey is the rarest of the chemical classics. Only seven copies have survived, all in public libraries. Dr. McKie has published this excellent facsimile from that in the British Museum. His introduction tells all known or likely to be known of this remarkable scientific miscarriage, which remained hidden from chemists until rediscovered in the time of Lavoisier himself.

Rey was born in Provence about 1582, and studied medicine at Montpellier, where he graduated as M.D. in 1609. He came of a family of small landowners and "tax-farmers." As Dr. McKie points out, "It is an odd coincidence that both Rey and Lavoisier were connected in this way with the fiscal system. Lavoisier's association with the Tax Farm cost him his life in the blindly revengeful hours of 1794." In this respect at least Rey was more fortunate. The occasion of Rey's *Essays* is the inquiry by an apothecary why tin gained in weight on calcination while lead decreased. Rey showed that in fact both increase. His work consists of 28 Essays, and the real crux is reached in Essay XVI, with Rey's "Formal response to the question, why Tin and Lead increase in weight when calcined." He says "this increase comes from the air, which in the vessel has been rendered denser, heavier, and in some measure adhesive, by the vehement and long-continued heat of the furnace; which air mixes with the calx and becomes attached to its most minute particles, as water makes sand heavier by moistening it and adhering to the smallest of its grains." The simile will not satisfy the modern student of chemistry, but at least it is based on sound experiment.

Before the days of scientific journals, intercommunication between men of science was maintained by a few leisured persons whose libraries served as central offices of scientific information. Very prominent among these men was Marin Mersenne (1588–1648), a Minorite father who lived in Paris. Rey's work impressed Mersenne, and the considerable correspondence between the two has survived. These letters give valuable information about the scientific life of their age. Dr. McKie reproduces them and thus renders his delightful little book of additional value.

CHARLES SINGER.

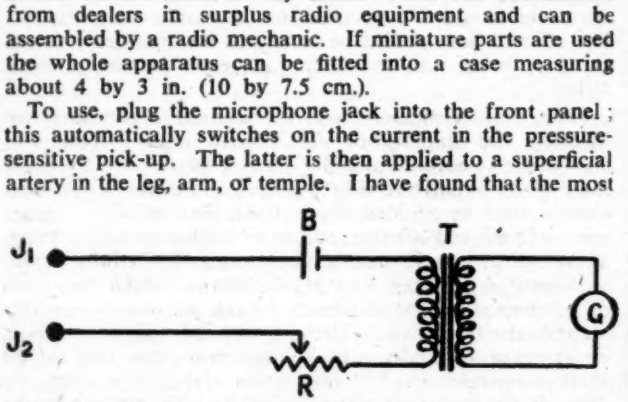
Preparations and Appliances

A SIMPLE PULSE INDICATOR

Dr. V. J. KEATING, lecturer in anaesthetics, University College, Jamaica, writes: The following is an account of a simple pulse indicator which has been found useful in neurosurgical and other prolonged operative procedures. The indicator may be employed, too, whenever a close and continuous watch on the pulse is required.

A small pick-up consisting of a carbon throat microphone element removed from its bakelite case is connected via a miniature transformer to a microammeter. The microphone is energized by a 4½-volt dry battery, the current being controlled by a resistance which varies the sensitivity of the apparatus. The flashlight battery will last several months, as the current drain is very small. Parts can be obtained from dealers in surplus radio equipment and can be assembled by a radio mechanic. If miniature parts are used the whole apparatus can be fitted into a case measuring about 4 by 3 in. (10 by 7.5 cm.).

To use, plug the microphone jack into the front panel; this automatically switches on the current in the pressure-sensitive pick-up. The latter is then applied to a superficial artery in the leg, arm, or temple. I have found that the most



J1 and J2: Terminals of a Post Office telephone jack or screw terminals for connexion of microphone leads. The terminal used is a small throat-type, about the size of a threepenny piece, removed from its bakelite cover. B: 4½-volt flash-lamp battery. R: A variable resistance of about 5,000 ohms. T: A miniature output transformer. G: A microammeter with full-scale deflection of about 50 microamps or less.

convenient method of securing the microphone is to place it under a blood-pressure cuff, which is then inflated to about 5–10 mm. Hg or less. If the instrument is used as an aid to recording the blood pressure a screw-type tourniquet is the best method for retaining the pressure head on a peripheral artery. It should be lightly applied, and is suitable for a relaxed patient only. No special skill is required to position the instrument, and a theatre orderly, nurse, or porter can be instructed in the simple procedure.

Cardiac irregularities, increase or decrease in the rate, are indicated at once and, with a constant setting of the sensitivity regulator, a change in the pulse volume too. The instrument is unaffected by diathermy and has been used to indicate a suitable time to take permanent E.C.G. records of cardiac irregularities under anaesthesia.

I have found this simple apparatus more reliable and useful than the complicated and expensive electronic pulse-rate-integrating counters.

Reports of Societies

CHILD MANAGEMENT

The Section of General Practice of the Royal Society of Medicine held their last meeting of this session on May 21, under the chairmanship of their president, Dr. J. V. Simpson. The subject of discussion was "Child Management," and, as at some of the previous meetings, was opened by a member of the Section, who was followed by two invited speakers, both in this case psychiatrists with a special interest in children.

Character Training

Dr. J. H. GIBBENS struck a controversial note early in his opening remarks by condemning psychiatric jargon and ridiculing the idea that children should never be suppressed or "repressed." He quoted a psychiatric report in which a child's objection to being washed with a certain sponge had been interpreted, to the child, in terms of phallic imagery, which he, the speaker, thought most deplorable. He limited his remarks to the management of the normal child from birth to the age of 7 as seen from the point of view of one who had observed children in general practice for 20 years, and excluded the problems of the mentally defective, the delinquent child, and the child severely handicapped by disease.

We were living in an age of revolution and change, when the foundations of everything previously thought stable and secure were being undermined, so that the proper management of children was very important. On what we believed and taught now would depend the future generation with all its potentialities for good and evil. The responsibility for care and management should rest with the parents and should not be handed over to nannies, grandparents, day nurseries, or psychiatrists; and the most important part of care and management was the forming of character. It was easy to produce good health and a good intellectual development, but the all-important development of character depended fundamentally on the care and on the teaching of the parents. Every tyranny which wished to divert or alter character tried first to disrupt the loyalties of home life. What were the desirable traits in a child's character? Courage, he thought, and sensitivity were the most important, and these could be taught, just as behaviour at meals could be taught. The idea that the child should not be disciplined and allowed to develop freely was both ridiculous and dangerous. The methods needed were kindness, a sense of humour, firmness, and an ability to let bygones be bygones. Character training should start at the age of 1, good behaviour being praised and bad habits frowned on when they first occurred. Most cases of behaviour problems as he saw them were due to lack of firmness or consistency in the parents, though it was true that in many cases proper care was made impossible by broken families, by the separation of children from family and home, and the appalling housing conditions which were so widespread to-day.

Behaviour Problems

Dr. E. BERESFORD DAVIES spoke of the management of behaviour problems. Though a large number of such cases were dealt with solely by specialists or in specialized institutions, there were many whose care was properly the responsibility of the general practitioner. Diagnosis was all-important, and it was necessary to distinguish between the neurotic child and the child with a behaviour disorder proper. Typically the neurotic child showed symptoms such as restlessness, night terrors, nail-biting, or somatic manifestations based upon anxiety and fear: such symptoms might well start or become no longer adequately hidden at the time of starting school. School was a great finder-out of weaknesses and proved to be the added test which exposed the insecurity in an unsatisfactory home.

The child with behaviour disorder, without psychosis, gross defect, or physical disease, usually showed some delinquent trends, though they might be very mild. By delinquency one meant broadly behaviour in reaction against organized society, which might be anything from bed-wetting to murder. The abnormal activity might be no more than misbehaviour or what might usefully be called "buffoonery"; its true importance must be judged by its effect on function and within the environment. One was struck in recent years by the surprising frequency with which abnormal E.E.G. tracings, particularly of epileptic type, were found in children presenting with behaviour disorder. Findings such as the ineffectiveness of even severe punishment, the eccentricity of parents or sibs, and the discovery of many red herrings in the history were enough to justify an E.E.G. examination. The child with the psychopathic type of disorder, though perhaps largely uninfluenced by punishment, nevertheless in the long run usually showed a respect for it and an immediate emotional reaction to it.

In treatment the establishment of transference—that is, effective emotional contact—was essential. Sometimes this might be done through a third party such as a social worker, a speech therapist, a school master or mistress, or a member of a religious or social group, while the general practitioner acted as adviser and court of appeal. Transference could often be begun and fostered by activity on the child's part, such as writing, drawing, painting, and playing. The child could seldom express himself save symbolically and could not explain his fears or think in abstract terms. One should not bribe children in treatment with material things, and one should try to insist upon emotional repayment: sudden, dramatic, or "miraculous" cures were usually dangerous failures.

The question of time was very difficult. How much time could be spared a week for treatment by the general practitioner? Even five minutes had been proved to be a real help and therapeutically effective. Ten minutes was better, 20 reasonable, and 40 or 60 were riches.

It was an important practical point to see and assess the parents, even to going so far as to "sort them out" before one expended much time on a child. In a personal case the analytical treatment of one of the parents had been a far better plan than the individual treatments of three of her five children. It was reasonable to look for disorder in one or both parents in all cases of psychological illness in children: if the parents were not causally connected with the child's illness they soon developed a disorder as a result of the abnormality in the child. It was also important to remember that the child often showed secondary complications of his illness through misunderstanding of his primary manifestations by his parents. Fear was the commonest single cause of neurotic illness: it might often arise from different teachings at home from those at school—perhaps a failure of teaching at home. The sexual field was a fruitful source of such trouble. Parents who ruled by fear were dangerous and, unfortunately, not uncommon. Sometimes one had to give the parent or parents a holiday from the child while one tried to instruct them in making a new start.

Stimulation, Security, and Consistency

Dr. ALAN MABERLY agreed with much that Dr. Gibbens had said about psychiatric jargon. Dr. Gibbens had noted that psychiatrists' children were sometimes very curious, but he had not, himself, found his own children more difficult than those of other people. He thought there were three important principles in child management. First was the principle of growth and maturation. The child required the maximal stimulus of growth to which he could respond in terms of physical, intellectual, and emotional development at any one time, and no two children developed in the same way or at the same rate. Secondly came the principle of security, physical and emotional, in the provision of which both parents played their part and should produce a balance. The mother-principle was protective and cautious and provided rather less stimulus than the child was capable of

responding to; while the father-principle was tough, adventurous, and outgoing. The Welfare State was essentially matriarchal with its emphasis on security and its dislike of effort and discomfort, the normal accompaniments of masculine strife and achievement. The third principle was consistency—frankness and honesty to the child and between the parents. All children put their parents on a pedestal and regard them as omniscient and omnipotent, even though they might see through their insincerities. The gradual breaking down of this was inevitable: it was part of growing up. The family doctor played a great part in maintaining the child's sense of security. He remembered him as the person who came when his parents, whom he thought knew everything, were puzzled and uncertain, and whose arrival dispelled the uncertainty and put everything right again.

Discussion

Dr. R. MACKEITH spoke of the great parental distress that was often caused by behaviour disorders in children and how very helpful simple advice and encouragement could be.

Dr. E. M. DIMOCK emphasized that child management should start with the first antenatal consultation for the first baby, for it was here that the doctor approached the family on health matters as opposed to disease or abnormality.

Dr. D. MORRIS said that generally the paediatrician saw cases only when things had gone wrong. Much could be done by organizing small groups of mothers at the welfare clinics, at which the approach to minor disorders of behaviour could be discussed.

Dr. L. BATTEN expressed some surprise at the opening speaker's statement that good health and good intellectual development were easily obtained. He thought the first was doubtful, and that children varied so widely in their development and character that a certain reasoned fatalism was the best way to regard the result of their upbringing. He thought that care and management could be overdone. One sometimes met children with admirable behaviour and all the desirable attributes whose parents had conspicuously neglected their upbringing. He thought, too, that flexibility rather than firmness should be the guiding principle. He agreed that the mother was the proper person to have full care of the child, certainly the first child for the first year; but it seemed to him that there was room for some regret at the disappearance of the nanny and the nursery, and especially the full nursery. He doubted whether courage or appreciation of beauty could be taught, though it was all too easy to teach fear and discourage sensibility.

Dr. J. ANDREWS said that happiness in childhood was certainly not always dependent on the amount of care. It was most unusual to hear a child cry in the conditions of extreme squalor and dirt prevailing, for example, in Algiers. He had noticed a tendency in parents to shelve the responsibility for dealing with behaviour disorders, saying, "It will be all right when he goes to school—the teacher will deal with it." There was also the modern difficulty of the only child who often failed in the struggle to satisfy the demands of mother's love and father's pride all by himself.

Dr. J. J. KEMPTON, speaking of the large number of behaviour problems seen in the paediatric out-patient department, recalled the words of Dr. Hector Cameron, who observed that the child tries to live up to what it believes to be its reputation. The mother would give a long account of how the child refused to eat, refused to sleep, and so on, the child meanwhile sitting by her with a look of approval on his face. There could be too much management, and certainly too much talk about management.

Other speakers mentioned the problem of the only child and also of the adopted child, with the special difficulty of explaining his adoption to him. The question was also raised whether corporal punishment was ever justified, the point being made that, while it was agreed that security was fundamentally important to the child, there could be no security without discipline.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Doctors and Heart Disease Research

SIR,—Special inquiries were sent recently from the General Register Office to all doctors in London and the Home Counties who certified the death of a patient, aged 40 or over, from cardiovascular, renal, or respiratory disease, during the first fortnight of March, 1952. The doctors were asked to provide additional information about their late patients in order to assist the Social Medicine Research Unit of the Medical Research Council in its studies of the prevalence of heart disease and hypertension in the population.

The response has been very gratifying, and we wish to thank the large numbers of practitioners who co-operated in the inquiry; there is no doubt that valuable information has been obtained.

However, the value of an inquiry of this type is much enhanced if something like 100% response can be obtained. We appeal, therefore, to any practitioner who received a questionary and has not yet returned it to do so now. In particular it would be helpful if doctors who have not returned the questionary because they no longer have access to the patient's records—for example, at the hospital where he died—would send the form to the hospital (to the medical registrar, for instance) for completion and return. If this is not practicable we should be grateful if the form were returned uncompleted to the first of the undersigned, with a note about the reason, at Kenworthy's Hydro, Southport.

As emphasized in the covering letter to the questionary, the method adopted for the inquiry fully preserves the confidential nature of the additional medical information being provided.—We are, etc.,

W. P. D. LOGAN.
Southport. J. N. MORRIS.

Epidemiology of Hypertension

SIR,—In your leading article (May 3, p. 962) you called attention to the study of blood-pressure data in populations as a means of throwing light on the obscure problem of hypertension. It may thus be possible to establish differences between those members of a population who develop hypertension and those who do not. Dr. J. Hambling (May 17, p. 1083) states that the hypertensive has a typical character structure and emphasizes the importance of mental stress in the development of hypertension.

Blood-pressure data on man in his most primitive state, living in communities most unlike our own, can usefully be compared with data from civilized communities. Ordman (*Clinical Proceedings* (Capetown, S. Africa), 1948, **7**, 183) has reviewed the incidence of hypertension in non-Europeans. Those with a traditional and primitive way of life tend to have especially low blood pressures with average values falling slightly or remaining stationary in old age, and hypertension and hypertensive illness are virtually non-existent. Data of this sort are available for Kenya negroes, Australian aborigines, Cuna Indians of Panama (Kean, *Amer. J. trop. Med.*, 1944, **24**, 341), and the Flowery Miao and Nosu

Blood Pressures of Male Malayan Aborigines (No attempt was made to get a basal value)

Estimated age in years	18–29	30–59	60 and over
Number studied	15	10	27
Mean systolic pressure in mm./Hg	114·8	111·6	109·8
Mean diastolic pressure mm./Hg	70·0	68·7	67·7

of China (Kilborn, *Chin. J. Physiol.*, 1937, **11**, 135). My own data on the Semai Senoi of Malaya are still fragmentary, but point in the same direction (see Table).

These data at least show that a rise in mean arterial blood pressure in a population is not an inevitable concomitant of old age. Such a rise of blood pressure may be limited to civilized communities which have existed for only a short time in man's history.

The causes of the apparent absence of hypertension in primitive peoples are obscure. Racial, climatic, nutritional, and psychological factors may all be important. The effect of non-genetic factors on hypertension is suggested by the contrast between the primitive tribal negroes of Kenya and negroes of South Africa and Central and North America, who have a high incidence of hypertension. The peoples discussed have mainly been dwellers in the Tropics, who, along with the white men in the Tropics, tend to have lower blood pressures than the white inhabitants of temperate zones. Starvation (Keys *et al.*, *Human Starvation*, 1950, p. 609) produces a lowering of blood pressure, and the findings in aborigines may have nutritional causes.

The Eskimos are of obvious interest in this respect, as these primitive people live in the frigid zone on a diet which used to consist almost entirely of protein and fat. Data on Eskimos (Bertelsen, *Meddelelser om Grønland*, 1940, **117**, No. 3, p. 104) suggest that blood pressures and the incidence of hypertension are similar in Eskimos and white men, though more than one investigator found an apparent absence of hypertension.

Speaking of Malayan aborigines, though their life is often beset with difficulty and danger, their ways of life have stood them in good stead in the past, and they expect them to do so in the future. They do not seem to have learned how to worry or to plan adaptations to new circumstances. They accept life fatalistically and their ambitions are limited.

Is it possible that these mental characteristics of primitive people, which are often so disastrous to their survival, may be a cause of their freedom from hypertensive disease?—I am, etc.,

London, W.11. IVAN POLUNIN.

Treatment of Hypertension

SIR,—In your issue of May 3, p. 933, Professor John McMichael enumerated a number of drugs which are or have been used in the control of hypertension. It appeared from his remarks that most of those which provide some measure of relief have unpleasant side-effects or are not without danger.

There is a very simple treatment which I have used for a number of years in any case of hypertension, without attempting to assess the cause, except, of course, noting any abnormal urinary excretion. The prescription is for 10-minim (169-ml.) doses of dilute hydrochloric acid in chloroform water, given four times daily *between* meals. The remedy was empirical, but the work of Selye, Hall, and Rowley (*Lancet*, 1945, **1**, 301) on experimental nephrosclerosis throws some light on the problem and may account for the benefit derived. Groups of rats, unilaterally nephrectomized, and then treated with compounds derived from the adrenal cortex developed nephrosclerosis and died. If in the water which these rats imbibed there was present ammonium chloride, then the rats remained healthy. Ammonium chloride in the body is presumably converted into urea and hydrochloric acid.

In practice the acid mixture is taken regularly for a matter of three weeks or a month, after which the blood pressure is measured again. If this has dropped appreciably the acid should be continued until the rate is stabilized, when the drug is given night and morning only or omitted altogether. The patient usually knows if the blood pressure is going up again and will ask for more of this apparently harmless medicine. In a certain proportion of cases the blood pressure will be unaltered after three weeks' trial. In that case it is useless to continue.

Below is a series of examples which includes all except three of those treated in this way, out of an alphabetically consecutive series of 800 case records. In the three omitted the result is not known.

Sex	Age	Before Treatment	Three Weeks to a Month Later	Stabilized
F	47	200/110	175/110	170/102
F	52	240/120	190/110	176/112
F	74	188/98	160/90	160/85
F	69	200/100	160/95	—
M	57	210/110	190/108	—
F	59	290/112	—	170/104
F	57	202/108	230/116*	—
F	59	170/100	140/90	140/90
F	74	185/115	180/104	—
M	72	210/116	168/106	170/110
F	51	190/120	210/130*	—
F	70	200/100	180/86	—
F	53	240/130	220/120*	—
M	55	210/108	190/118	—

* Treatment failed. Discontinued.

Dr. Helen Taylor has kindly provided me with records of five more cases. These show the same reduction, which was quite substantial even after one week.—I am, etc.,

London, W.1. H. WARREN CROWE.

SIR,—In connexion with the excellent article by Professor John McMichael on "Management of Hypertension" (May 3, p. 933) and the leading article on "Epidemiology of Hypertension" (p. 962), I would like to put some observations on record and lay them open for discussion.

Referring first of all to the application of the term, the author states that a rise of the diastolic pressure above 90 mm. Hg must be described as hypertension. While this is the correct teaching, I think many readers will agree with me that hypertension is becoming so common in adults, even under 40, that the majority of people can now be classified as hypertensives, and I have often wondered whether our conception of hypertension should not be revised. I want to mention particularly that my observations are not only based on readings taken in the surgery or at the sick-bed, but also on routine examinations on apparently healthy individuals employed in an engineering factory. I also find higher readings in expectant mothers.

Regarding the question of treatment, I have for many years practised the therapy of venesection. Although I have not seen appreciable reduction in the actual pressure readings, the procedure was usually followed by a symptomatic relief, which may be due not so much to lessening of the tension as to replacement of the blood volume with tissue fluid and thus lowering the tendency to thrombosis. I must say that I have not seen strokes following venesection as they happen after medical reduction of blood pressure. A method similar to venesection is the application of leeches, which has become popular again in France, owing to the anticoagulant action of the leeches more than the actual loss of blood.

As for the "Epidemiology of Hypertension," I rather like this term, as, like several of my colleagues, I have noticed, at certain times of the year—more so in the winter, but also during thundery periods in the summer—an increased tendency to strokes. All hypertensive patients seem to have a "bad time" during that period. It might be interesting to compare readings of blood pressure with those of the atmospheric pressure or humidity in the air.—I am, etc.,

Spennymoor, Co. Durham. E. BRAUER.

Ethyl Chloride for Unconscious Hysterics

SIR,—The immediate care of an unconscious patient who has suffered a hysterical fit frequently presents an annoying problem to the staff of the hospital casualty department. These cases will usually recover consciousness if allowed to sleep it off in their own good time, and occasionally their immediate recovery can be brought about by such means as the inhalation of ammonia fumes.

Towards the end of the last war, while working in the casualty department of Sydney Hospital, I developed the following technique for dealing with these patients, which perhaps is not original but is certainly not in common use.

The technique consists in administering a very light anaesthetic with ethyl chloride (early stage I of anaesthesia only) and at the same time conveying words of reassurance and encouragement. Usually, during this procedure the patient will regain consciousness abruptly, but on occasion it has been found that while under the influence of the ethyl chloride the patient was accessible and would reply to questions. Nevertheless, as the anaesthetic wore off the ability to respond would be lost. In such cases continued persuasion for a few minutes during light anaesthesia was all that was required to return the patient to consciousness. In two cases unsuccessfully treated, a diagnosis of catatonic schizophrenia was made subsequently. Ethyl chloride is superior to other anaesthetic agents for this type of psychiatric first aid, because, with the small dose administered and the rapidity of recovery from it, patients may be permitted to leave the hospital within an hour or so of commencing treatment, provided, of course, that they are accompanied. They are instructed to see a psychiatrist in order to receive more definitive treatment.

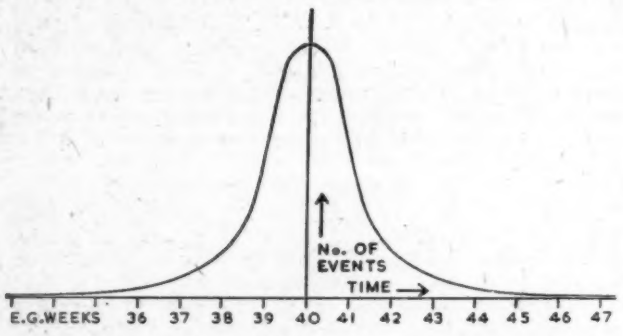
—I am, etc.,

Sydney, Australia. DAVID MONK ADAMS.

Period of Gestation

SIR,—In their paper (May 3, p. 938) Drs. Thomas McKeown and J. R. Gibson have missed a golden opportunity to show how by proper statistical treatment one can make far-reaching conclusions from limited data. This is surprising, since in their previous paper, to which they refer, they make a promising start on such treatment. Legal counsel are liable to ask, "Could this unusually long gestation have been a one-in-a-million chance?" No one has collected a million cases, and there is no value in giving the longest period in a few thousand cases—viz., "with fair confidence" 328 days—when longer periods have already been accepted by the courts. Yet, by proper treatment of the same data, the probability for any hypothetical period could be given, together with a numerical estimate of one's confidence in it. For non-mathematical readers the basis of this is simply explained as follows.

Whenever the succession of one event upon another (e.g., labour upon conception) is dependent not upon a single exact process but upon several variable processes, the time of the second event may be expected to be variable. Moreover, if the number of disturbing factors is extremely large we can give the distribution of times to be expected. It is the "Normal" or "Gaussian" curve, the shape of which is roughly as drawn.



It is especially to be noted that a few events are to be expected to occur at times far from the range which includes the main body of them. They are not on that account to be treated as abnormal or rejected as bad observations. Indeed, if they are absent the statistician will justly suspect that someone with less understanding has selected the data, suppressing some on arbitrary grounds.

The proper treatment of the data in this case would therefore have been to fit a normal curve and read from it the probability of any given long period. The authors showed in their previous paper that a normal curve cannot be fitted to the whole distribution from 28 weeks upwards. That was only to be expected: we know many distinct pathological conditions tending to cause premature labour. These eliminate themselves by the 40th week, so it is to be expected that a half-curve would fit the data from 41 weeks upward. It does so very well, showing incidentally that "post-maturity" is not a distinct pathological condition, only an extreme example of the normal. Armed with such a curve, we could tell the courts not just that one case in a certain series of 18,000 went to 328 days, but that, say, 14 to 18 in every million are expected to carry beyond 48 weeks (or whatever the figures should turn out to be).

I have held for some time that the "basic science" of medicine is not physics or chemistry (much less zoology or botany) but statistics. In physics the beginner is encouraged to get exact results, and only later is variability admitted. This is bad preparation for biological studies, where one must from the start know how to get results despite, and even because of, variability. If doctors were thus taught we should cease to hear the sneer with which a certain sort of clinician produces his "exceptional case" to confound the physiologist, and both would appreciate the truth of that much-abused saying, "The exception proves (i.e., tests) the rule."—I am, etc.,

Northampton. A. B. PARTRIDGE.

Continental Views on Leucotomy

SIR,—I was very much interested in your excellent leading article (April 26, p. 909) and the pro and con correspondence that has opened. Opinion is by no means unanimous on the matter, and I thought British readers would be interested in the views of their Continental colleagues. The Swiss fortnightly, *Médecine et Hygiène*, of Geneva, has recently (February 1 and 15, March 1, Nos. 211–213, 1952) conducted an open international forum on prefrontal leucotomy, the result of which is most instructive and quite representative of Continental thought.

The contributors, all authorities on the subject, had been asked to express their views on the following questionary:

1. Can psychosurgery be put on the same level as surgical operations which enjoy unanimous approval?
2. Does the operation on the frontal lobes not present the danger of transforming a functional disease into a non-reversible organic one?
3. What are the favourable results of the operation?
4. What are the medico-legal problems arising from the operation?

(*a*) Whom does the decision to operate depend on: the neurosurgeon or the psychiatrist? Eventually should the decision to operate be left to a corps of experts, as for legal abortion?

(*b*) How should the consent of a psychically impaired patient or of an incompetent family be obtained? and

(*c*) What will the civil or penal responsibility of a leucotomized person be?

Space does not allow me to go into a detailed account of each author's opinion on every one of these problems, and I will only summarize the general conclusions that can be drawn from their divergent but most instructive points of view.

Of 12 answers six are absolutely in favour of prefrontal leucotomy (Lhermitte, Paris; Cossa, Nice; Wertheimer, Lyons; Freeman, Washington; Bersot, France; Feuillet, Nancy). Two are equally absolutely against it (Morel, Geneva; Baruk, Paris). Four are favourable but with some reserve (Buffat, Lausanne; Hoch, Bâle; Porot, Algiers; Schneider, Lausanne), and one is of a purely legal character (Naville, Geneva). Therefore it can be concluded that tendencies are rather favourable for the operation.

All contributors are unanimous in pointing out that leucotomy should be undertaken only after a long application of all the other methods of treatment without success; that it is indicated only in cases with no tendency to healing and presenting behaviour incompatible with social life or dangerous to the individual (suicidal).

The discussion on the *functional* and the *organic* shows that such a distinction is far from being absolute or even well defined. The same applies to the non-reversibility of the surgical lesions. Morel is absolutely categorical about this point: for him the enormous quantity of fibres cut off from their circuit leads to a secondary degeneration of the cortical neurons afferent to the sectioned fibres. On the contrary, for Wertheimer this degeneration does not take place, thanks to a system of short fibres of association.

Behaviour troubles do not seem to be considered as being of a grave nature—even by those opposed to the operation. If the characterological elements do undergo a change, this seems to be towards a favourable rather than a negative turn.

As for the *medico-legal* problems, everybody agrees that it should be the psychiatrist who takes the final responsibility of deciding on the operation, but with the consent, if not of the patient, at least of his family or guarantor. On the other hand, though some do suggest a body of experts, the idea of giving it authority other than advisory (as in legal abortions) would *a priori* treat leucotomy like a criminal act. Concerning the legal responsibility of the leucotomized individual, it is variable in proportion with its gravity as established by a college of experts.

The overall conclusion that can be drawn from this Continental forum is that in view of the absence of other treatment one is bound to accept it, at least for the moment and until better methods are instituted, as being the only medical act susceptible of opening a door of salvation to patients hitherto confined to a lamentable existence.—I am, etc.,

London, E.9. S. A. GUEUKDJIAN.

Discharge of Certified Mental Patients

SIR,—While agreeing with Dr. Otho FitzGerald (May 17, p. 1082) that there are advantages in allowing to the nearest relative the power of ordering a certified patient's discharge, I must endorse Dr. C. R. Birnie's plea (May 3, p. 971) for an alteration in the law in this matter.

Dr. Birnie has mentioned two undesirable results of the present arrangement: First, premature discharge with consequent relapse; and, secondly, the liberation of patients who, though not technically "dangerous," may be an intolerable nuisance in the community. A third and, to my mind, an even more important consideration is that discharge may be effected by a relative who is quite unfit, unable, or unwilling to give the patient the further care he may need. The following are examples:

A. Patient a chronic schizophrenic woman. Sister develops a paranoid psychosis, visits the hospital, and insists on taking the patient out. My advice to the contrary (verbally and in writing) is overborne by advice which the sister receives in hallucination (she says, from me). Patient is taken away and forced by sister to have osteopathic treatment; resists and makes scenes and eventually is returned to hospital, very indignant with sister. Fortunately I am able to induce her to become a voluntary patient, so that sister loses her power over her and she remains happily in hospital.

B. Folie à deux in brother and sister—both in hospital. Brother escapes and after 14 days is automatically discharged. He then orders sister's discharge.

C. Senile paranoid woman, the despair of all welfare agencies and institutions; no one will take her except the mental hospital. Brother in America, knowing nothing of facts, writes angry letter—she is sane and must be discharged. Board of Control rules that he has the power to discharge—there is no residence qualification!

The law in fact is farcical. If a patient is being cruelly treated or neglected the public authorities have power to remove him to hospital; but no sooner is he there than the same relative who has been guilty of this neglect or cruelty can insist on taking him away again.

What is needed here is a simple addition to the grounds on which a barring certificate can be given by the medical superintendent—namely, that he has reason to believe that the patient will not receive proper care. The relative would have, as now, a right of appeal to the management committee and, if he wishes, to the Board of Control.—I am, etc.,

Coulsdon, Surrey. ALEXANDER WALK.

SIR,—By a strange coincidence, after reading the recent correspondence (May 3, p. 971; May 17, p. 1082) about the discharge of certified mental patients, I met a case of a psychiatrist whose "clinical prestige" appeared to have been somewhat deflated by the patient leaving before being subjected to "advice" or "stronger methods of dissuasion." A few days ago I was consulted by a woman aged about 40 who was depressed, agitated, and obviously mentally unwell, though not suicidal. She had walked out of her mental hospital (where she had been a voluntary patient for nine months) the previous day, as she was concerned about the children at home. She realized, however, that she was incapable of looking after her home and her family, and wanted to return to hospital. She said that the hospital doctor would not take her back unless certified, but she and her family wished to avoid the stigma of certification.

I rang up the doctor concerned, who confirmed that he would not have her back unless certified, although he would not give his reasons over the 'phone. When I emphasized the patient's desire to avoid certification, his comment was, "Then she should have thought of that before she walked out." Such was the understanding of his patient by this alienist. The medical superintendent, whatever may have been his own views, felt compelled to support his colleague. It appears, therefore, that my patient will have to be certified before she is allowed to return to the hospital.

Does this paradoxical situation then make "less nonsense of the complicated machinery of certification"? We might say, with Don Juan: "A strange coincidence, to use a phrase, by which such things are settled nowadays."—I am, etc.,

London, W.13. AARON LASK.

SIR,—Dr. C. R. Birnie has raised a very interesting problem. He ends his letter (May 3, p. 971) with the words: "In particular, it is unsatisfactory to continue to allow 'the nearest relative' to be the arbiter of the patient's destiny." I think it should be pointed out that such responsibility is sometimes thrust upon the unfortunate next-of-kin by the hospital authorities themselves.

Certified patients are sometimes sent home on a month's trial. This is an excellent scheme which does allow some assessment of how the patient is going to react to his environment outside the hospital. At the end of the month, however, the nearest relative becomes the arbiter of the patient's destiny. He has to decide whether or not to keep the patient at home, often in the face of all the moral blackmail which the patient can exercise through an hourly repetition of, "I will never forgive you if you send me back." Surely this imposes a quite unfair burden of responsibility on the next-of-kin, as well as being thoroughly illogical. Surely the decision as to what should happen to the patient should rest with the psychiatrist in charge of the case, after he has questioned both the patient and the next-of-kin separately.

The psychiatrist might also derive some help from the family doctor, who should have been observing the patient while on leave. For this liaison to work effectively, the general practitioner would have to be informed of the patient's discharge, a courtesy which to-day is frequently overlooked.

In psychiatry more than in most branches of medicine there is a great gulf fixed between the consultant and the general practitioner. If there was more liaison and co-operation much more could be done to alleviate these problems. If the general practitioner was approached by the psychiatrist he might help to dissuade relatives from exercising their rights under Section 72 (3). After all, the family doctor has had to perform the unsavoury task of certification, assisted by the evidence of the nearest relative. They have both shared a very unpleasant experience. The family doctor is thus in a position to remind the next-of-kin of this, and at the same time he can point out that, if such a step was necessary again, it would be even more disagreeable. It sometimes happens that, while awkward relatives view the psychiatrist with suspicion, they may accept as unbiased the advice of their own family doctor.

While closer co-operation between consultant and general practitioner is not the complete answer, it would help in certain patients. In any case a better liaison between these two branches of the profession is long overdue.—I am, etc.,

Leicester. C. A. H. WATTS.

Copper Content of Foods

SIR,—The report of the Food Standards Committee's Metallic Contamination Subcommittee which refers to the presence of copper in foods seems to contain some anomalies. In general one would think that the foodstuff consumed in greatest amounts would be permitted to have only the lowest amount of copper, but we find that tea, a universally consumed beverage, is provisionally permitted 150 p.p.m.,

and cocoa powder (which is widely used in drinks for children) is permitted 70 p.p.m., whereas flavourings, tomato ketchup, yeast and yeast extract, which are consumed in minute amounts compared with tea and cocoa, are restricted to 30 p.p.m., 50 p.p.m., and 30 p.p.m. respectively. Furthermore, tomato ketchup is only permitted 50 p.p.m., but tomato purée is permitted 100 p.p.m. Why this discrepancy? In the case of both these tomato products the permissible copper is calculated on a basis of solids. Are yeast and yeast extract calculated on this basis too, or on a net weight basis?

The high value permitted for tea is said to be due to the fact that copper fungicides are used for spraying tea plants in Ceylon. Such a copper content is either safe or it is unsafe. If the latter, then it is both unwise and dangerous to accept such a high copper content; if it is not, then the logic of insisting upon much lower limits for many foods consumed in infinitely smaller amounts is impossible to follow.

One other point is that a higher copper content than 20 parts per million in shellfish and crustacea is acceptable if it is of natural occurrence. Why is tea allowed 150 parts when most of the copper is not natural?

It may be that the subcommittee has the best possible reasons for making these apparently invidious distinctions, but I must confess to being very curious as to what they could be.—I am, etc.,

London, E.1. G. H. BOURNE.

Skin Lesions in Ulcerative Colitis

SIR,—I was most interested in Mr. W. B. Gabriel's account of surgery in the treatment of chronic ulcerative colitis (April 26, p. 881), especially in his statement that "spreading ulceration of the skin is not likely to respond to treatment except by ileostomy and colectomy."

We have at present in this hospital a woman aged 38 years, who has had severe ulcerative colitis for the past five years. She has refused surgical treatment several times and has had numerous periods of relapse with eight to ten fluid stools daily and much blood and mucus per rectum. On December 21, 1951, a pustular eruption appeared on both legs, and on the left elbow, which rapidly became confluent and developed into an extensive phagedenic ulceration with complete sloughing of the skin, exposing subcutaneous fat and deeper tissues over the whole of the legs from ankles to knees and posterior aspect of both thighs. Apart from one week's dressings with zinc peroxide cream no specific therapy seemed of any help and she has now completely healed with simple saline baths and tulle gras dressings, and very occasional "eusol" dressings to clear superficial *Staphylococcus aureus* infection.

—I am, etc.,

Carshalton, Surrey. ISABEL G. SMITH.

Tuberculosis Incidence in Children

SIR,—We are interested in the findings reported in Dr. A. W. Dickie's paper (March 29, p. 682). Lesions were, it is stated, found in all the child contacts who had not previously received B.C.G. vaccine, although in one boy aged 11 the primary complex is described as only "suspect." Our experience in this country (*Lancet*, 1951, **1**, 1116) showed that only 36% of 518 children aged up to 15 who were living with bacteriologically positive tuberculous adults had positive tuberculin reactions when first examined as contacts. This is in marked contrast with the 100% in Sweden reported by Dr. Dickie, and one wonders whether his families may have in some way been specially, although unavoidably, selected—or whether the apparent difference is due to the aetiological factors of childhood tuberculosis not being the same in the two countries.

In four Swedish cases tuberculin conversion was known to be recent, and in 17 others recent conversion was presumed from the condition found, and all 21 became clinically ill. Of 101 tuberculin conversions reported by us only 18 children developed lesions, the majority radiological findings of no very serious significance, but three became ill (two developed meningitis). It is remarkable, however, that 80% of our children underwent conversion of their tuberculin reaction without clinical illness. The disparity between the Swedish and British findings may be due to differences in the clinical manifestations of tuberculosis in different places, or to different criteria of what constitutes clinical illness in primary tuberculosis. It is often puzzling to assess whether or not hilar shadows are, in fact, enlarged on *x*-ray examination, and in a doubtful case it is difficult not to be influenced by the tuberculin reaction if its result is known. From the descriptions given, it is impossible to be certain, but seven of Dr. Dickie's children may have been this type of hilar adenitis. The information given, however, suggests that about half of the 21 cases were quite ill, although the type of disease was one which, in this country, would usually have a fairly good prognosis even in the absence of treatment.

It is interesting to learn of the marked difference between the 22 B.C.G.-vaccinated and 22 unvaccinated Swedish children in their reaction to exposure to tuberculous infection. The findings, though the numbers are small but probably collected with difficulty, are nevertheless impressive. Without actual trial, it is difficult to know whether similar results can be obtained in this country.

—We are, etc.,

Edgware. H. J. TRENCHARD.
R. GRENVILLE-MATHERS.

Intra-articular Streptomycin

SIR,—We would like to make the following points in answer to the letters by Mr. J. A. Cholmeley (May 3, p. 974) and Mr. G. Blundell Jones (April 5, p. 766): (1) Two out of our 10 cases, both of which were proved by biopsy, still have normal knees three years after treatment. (2) One of these cases had been treated for a period of five years by recognized conservative methods, without any benefit, whereas the method of treatment described has now resulted in an apparently normal knee-joint so far. (3) The series is admittedly small. Before the use of streptomycin an occasional cure was claimed in early synovial tuberculosis of the knee-joint in children by conservative methods alone. This entailed prolonged hospitalization, often from one to two years, followed by a further long period in a calliper. In neither of the cases mentioned above was splinting continued longer than three months.—I am, etc.,

Windsor. G. P. ARDEN.

Pneumoencephalography and Fits

SIR,—Major John Marshall and Dr. C. W. M. Whitty (April 19, p. 847) suggest that "the diagnostic value of pneumoencephalography in young adults with epilepsy as their only abnormality is not great." May I point out that this conclusion is based on one particular method of pneumoencephalography? The method described does not give all the information obtainable by air studies. In order to obtain the maximum information two steps are necessary: (1) replacement of cerebrospinal fluid by air must be as complete as possible: *all* the fluid obtainable must be replaced by air. (2) The radiographic examination must be *repeated 24 hours after* the first set of films has been taken. These *second-day* pictures, taken in the erect posture, may reveal abnormalities not revealed by those taken immediately after the insufflation of air. One must follow the air as one follows a barium meal.—I am, etc.,

Dublin. ADAMS A. MCCONNELL.

Skin Banks for Wartime

SIR,—I have only just—through force of circumstances—read your leading article (November 3, 1951, p. 1073) and Mr. W. J. Dempster's paper (p. 1041). Certainly a very large amount of research work has been done both in England and America on this subject, during the war and since, but the total outcome has been "All homografts failed" (except Mowlem's method of alternating autografts and homografts, and there would appear to be a limit to this). No one, however, seems to have raised this very important point: if skin homografting could be made successful, would the method be practicable, at least on a large scale, in the event of emergency?

For the next war would be obviously one of bomb, blast, and burn, in which vast areas of skin in the aggregate would be lost

by the civilian population. If these areas are not grafted very quickly large numbers of people will die, all hospitals will be choked with such cases in all stages, and cross-infection will be rife.

If homografts are used several donors may be necessary for each case. In a recent case in America nine donors were necessary for one case; it is said three theatres were used, with all accompanying staffs of surgeons, anaesthetists, and nurses. Multiply that by hundreds of such casualties in one night and one can see at once the impracticability of the method, even if only two or three donors were necessary for one case. Not all donors could be sent home immediately; beds would have to be found for them and dressings done. There would soon be difficulty in finding donors, especially when it became obvious that under emergency conditions many donor areas would inevitably become infected and cause disability for some time, the areas sometimes becoming keloid after slow healing. There would be so much to do that general surgeons unaccustomed to the technical difficulties of such work would of necessity have to undertake a large proportion of the cases, and donor areas might be sacrificed in vain. Every square inch of the patient's own skin may be required to be conserved for subsequent repair of face and neck and around joints. Radiation of donors or the giving of cortisone or A.C.T.H. to patients in large amounts are equally impracticable and of doubtful wisdom.

Last October I published a paper "On the Possibility of Establishing Skin Banks" (*Brit. J. plast. Surg.*, 1951, **4**, 157) in which I advocated the development and use of cultured epidermis for such cases. This is believed to be possible if those with unlimited laboratory facilities would take up the work.

There are three tissues (apart from blood vessels) which are homotransplantable—cornea, cartilage, and lens—and they are all three *avascular and non-antigenic*. They are non-antigenic because they include considerable amounts of a polysaccharide, similar to that contained in the capsules of pneumococci. (For this see the valuable work of Bacsich and Wyburn in *Proc. roy. Soc. Edinb., B.*, 1947, **62**, 321, which seems to have escaped Mr. Dempster). Cornea, which is a modified epidermis, is homotransplantable without any preliminary tests for compatibility, either as full-thickness grafts or as split grafts.

In my paper methods are suggested whereby small sheets of epidermis could be cultured on fibrinized nylon or semipermeable membrane. As a source for initial seeding, cornea or scrapings from early foetal skin is suggested. Once started and handed to the geniuses of production *en masse* it should proceed just as dramatically as penicillin did. Centrally stored and refrigerated sheets of epidermis (about 3×4 in., or 7.5×10 cm., would be a convenient size) could be distributed over wide areas by aeroplane—I am, etc.,

Wellington, New Zealand. H. P. PICKERILL.

Barrier of Silence

SIR,—The University of London has established a department of Social Administration under Professor R. M. Titmuss. I thought I knew what "administration" means, but it seems that I did not. At any rate, Professor Titmuss, apparently seeing no room for improvement in administration, finds himself free to turn his attention to medical ethics, and in particular to the behaviour of consultants towards hospital patients. According to Press reports he has conducted a systematic interrogation of ex-patients and has tabulated their experiences:

"Patients complained more than anything else that 'no one told me anything. Nobody asked me. I do not know.'"

"A woman patient had said that she was examined in complete silence. In the ward, she found one of the biggest worries was whether or not patients were to have abdominal operations."

To Professor Titmuss the allegations, some of which at least are obviously untrue, frivolous, or hysterical, are evidence of a barrier of silence deliberately erected "to maintain authority" (of all silly reasons). "If," he said, "one analyses the result of hospital experiences of ex-patients, it is interesting how often this complaint of the discourtesies of silence recurs. Why is it not understood that courtesy has a therapeutic value?" (*The Times*, May 12).

"Florence Nightingale," he went on, "understood that the sick suffered mental pain almost as much as bodily pain" (*Sunday Times*, May 11). Professor Titmuss thinks that the doctors are ignorant of this truth. I do not pretend to more than a fraction of the extensive knowledge of medical history possessed by the learned professor, but according to my recollection it was against the administrators that Florence Nightingale's vehemence was mainly directed.

We may allow that in some complaints there may be an element of reason, but there are right and wrong ways of dealing with them. As I understand the situation the metropolitan teaching hospitals are part of the Faculty of Medicine in the University. The behaviour of members of this Faculty is now the subject of a clandestine inquiry by another Faculty, and the adverse result announced to the public. This is a matter of university ethics which, I respectfully suggest, the Senate would do well to consider.

This inquisition being a matter which affects the whole profession, we are entitled to know more about its conduct. How many patients are being questioned, how are they being questioned, and how are they selected? Professor Titmuss no doubt has a black-list of medical offenders. May we be allowed to see it? We are subjected to quite enough snooping without the universities joining in the merry game. In my opinion Professor Titmuss could not have chosen a better method to foment discontent, to encourage querulousness, and to aggravate tension in a relationship already strained by nationalization.—I am, etc.,

Cambridge. FFRANGCON ROBERTS.

SIR,—May I draw attention to a short report in the *Sunday Times* (May 11) of a speech by Professor R. M. Titmuss, in which he criticized members of hospital staffs for not giving the patients more information concerning their illness? I fear that this criticism is more than justified in some hospitals. Now that the level of education in the country is rising, and more intelligent patients are being admitted to hospitals under the 1946 Act, this question is of real importance. I agree with Professor Titmuss that such information is part of the patient's treatment, and a very important part, which should be taught to every student.—I am, etc.,

London, W.14. MALCOLM DONALDSON.

Fouling the Nest

SIR,—I am very much in agreement with your correspondent (May 3, p. 974) who draws attention to the fact that the standing of the medical profession in the eyes of the public must be affected by the low opinion of their colleagues so often publicly expressed by distinguished medical men.

A deplorable example of this nature recently occurred in Sheffield. The *Sheffield Telegraph* reported that Dr. Stephen Taylor told members of the Institute of Hospital Administrators (Sheffield region) at a week-end school that patients were far too humble with doctors. Dr. Taylor is a member of Harlow New Town Corporation, a former assistant editor of the *Lancet*, and ex-Socialist M.P. for Barnet.

He added: "That's one of the great troubles in our society—treating doctors like gods. They aren't; they are just human beings with inflated egos. They take very high cash rewards as a matter of course, little realizing that many people in the world do work just as hard and just as difficult for a quarter of their salary. Doctors by and large know very little about humanity—they lead a most sheltered life. They see patients at their best." The report goes on to state that a "statement made by Dr. Taylor that hospital administration demanded little specialized knowledge" was challenged by Mr. Trusson, so Dr. Taylor appeared to be having a good afternoon.

One wonders whether Dr. Taylor was speaking with his tongue in his cheek or whether his remarks were prompted by loyalty to members of his political party, who have for so long shown their absolute contempt for our profession. At all events such reported utterances made by one doctor

about others are most painful and serve to show the lack of loyalty and unity which will eventually undermine our integrity as a profession.

Any general practitioner will know how humble people are if they don't get all the medicines, certificates, orders for corsets, extra coal, and priority for washing machines that they demand. The "very high cash rewards" we receive have always worried Mr. Bevan, and I concede that the recent findings of the Commission appointed by the Government to investigate our payment must have been very sick-making to Mr. Bevan and his supporters.—I am, etc.,

Sheffield. E. C. ATKINSON.

SIR,—I am grateful to you, and to Dr. Atkinson, for giving me this opportunity to deny both the intention and the substance of the remarks imputed to me by the *Sheffield Telegraph*. The quotation is an ingenious paraphrase, torn from its context, which is as distasteful to me as it is to Dr. Atkinson. Fortunately, the substance of my speech will be published shortly, and I will make sure Dr. Atkinson receives a reprint. I hope he will find there something of value to our hospital service, and to the understanding of the many real difficulties which often arise between doctors and lay administrators.

I have no wish to make a political reply to Dr. Atkinson, the more so as I happen to be a personal admirer of his work. I cannot speak for my party, but at least let me say personally that I feel no contempt but rather a humble admiration for the work done by the many general practitioners it has been my privilege to visit in the past 18 months.—I am, etc.,

London, N.7. STEPHEN TAYLOR.

Damnable Heresy?

SIR,—As a general practitioner interested in the future of domiciliary practice and in the education of students on which that future depends, I was delighted to read Dr. J. Vernon Braithwaite's outspoken letter "Damnable Heresy?" (May 3, p. 974) and also Dr. D. M. MacManus's suggestions for "Improving General Practice" (May 10, p. 1030).

I was a student at the time professorial units developed, and they were rightly welcomed for their ability to co-ordinate teaching and to see that the full range of the curriculum was covered. I learned very little from the professorial unit, but a great deal from the practising physician who had started work as a schoolmaster in Australia, taken his fellowship in surgery, and finally turned to medicine, and from men like Dr. Braithwaite who had developed a consulting practice after apprenticeship in general practice.

All students should be introduced to the high scientific ideal in medicine—and this is a special duty of the professorial unit. More than half the students, however, are destined for general practice. For them the high scientific ideal will become a distant light guiding them as they struggle with the realities and the perplexities of work in the homes of the people. Any tendency to make teaching more academic can only make life more difficult for them and worse for their patients.

What is needed is a large proportion of teachers who have been in general practice for not less than six months or a year, and who know vividly the plight of the patient ill at home, the anxieties of his relatives, and the practical problems which face the general practitioner. Such men will know, for example, the case of coronary thrombosis not merely as an E.C.G., a total cardiac diameter, a series of blood-pressure readings, and a blood-urea report. They will remember the man lying in anguish, wrapped up in winter clothes, on the floor of the unlit garage with the starter-handle on the concrete floor beside him. The man who, from actual experience, can combine these pictures can teach the future general practitioner.

Dr. MacManus mentions the Guy's system of one or two lectures given by general practitioners at the end of the course. That is good; particularly if it does not degenerate into a list of certificates, and tips on how to cope with the executive council.

Two advances have recently come to my notice. One teaching hospital is making the experiment of sending final-year students to live and work with general practitioners for a month. This will show them the domestic problems of both doctor's family and patients, the emergencies which later become hospital teaching cases, the trifles which waste time, and the chronics and neurotics who never reach hospital.

The other experiment, made by a different teaching hospital, is that of asking general practitioners to go on physicians' ward rounds and present the general practitioner's point of view of cases demonstrated by the physician. This gives the students a picture of the whole illness in proportion and an idea of what will be expected of them before and after the patient's time in hospital. These methods are much to be encouraged.

It is true that many students are unfitted mentally, temperamentally, or physically for the life of a general practitioner, and they rightly aim at a consulting or research career. It will do them no harm to spend a year at the battlefront; and when they come to teach they will have a real knowledge of the life they left behind them.

Any tendency to recruit more and more professors from more and more purely academic types is indeed—as Dr. Braithwaite says—a damnable heresy. Those who hold it must go to the stake: because our children must have practical men to befriend them in their homes and guide and help them in adversity.—I am., etc.,

Wembley, Middlesex. M. C. ANDREWS.

Is Illness Inevitable?

SIR,—At the recent Health Congress of the Royal Sanitary Institute, Dr. Andrew Topping, Dean of the London School of Hygiene and Tropical Medicine, is reported as having said that "a very large proportion of the public looked upon illness and disease as something inevitable. That was all very well before the bacteriological age, but nowadays, when the ultimate exciting cause of practically every disease was known, the persistence of this idea of inevitability was ridiculous" (*Journal*, May 10, p. 1021).

I have seen similar statements reported in the medical and lay press before, and I have seen reports of criticisms made by Dr. Topping of the public and the medical profession for their reluctance to pay attention to the preventive side of medicine. This leads me to ask for the courtesy of your columns in order to put two questions. First, is it in fact true that "the ultimate exciting cause of practically every disease is known"? Do we know the cause of cancer, coronary thrombosis, hyperpiesia, peptic ulcer, rheumatism, the blood diseases, diabetes—the list could be prolonged indefinitely? And, secondly, what is this advice about sensible living which Dr. Topping asks us to give to our patients? Apart from repeating a few platitudes about regular hours, fresh air, exercise, and avoidance of excess, what are we in fact to tell the patients who flock to our surgeries with a host of complaints which they would be glad to avoid if we could tell them how? I do not know how to prevent the common cold, measles, boils, rheumatism—in fact, it would be much easier to enumerate those diseases which we *do* know how to prevent.

Surely the successes of preventive medicine in the past and the hope of its success in the present lie much more in national and local action in such directions as housing and education than they do in the approach made in the doctor's surgery.—I am, etc.,

Manchester. BASIL LEE.

Treatment of Acidosis

SIR,—I have found a satisfactory method of treating acidosis, or fat intolerance, and I am wondering if any of your readers have tried it. It is satisfactory for the child who is unable to tolerate fats without frequent loose pale motions which float on water. The child gets thinner and the abdomen distended. Dietetic variations only alleviate the condition temporarily, and certainly do not encourage a gain in weight. I use a vitamin-B whole complex three times daily and a decrease in the fat intake for about a fortnight. After this full fat complements can be given and the vitamin-B intake gradually reduced.—I am, etc.,

York. F. CHARLOTTE NAISH.

Trapping the Surgeon's Sweat

SIR,—A good deal of honest sweat is shed by many surgeons, and that from the forehead may drip into the wound or bedew spectacles. Moreover, trouble and even alarm are caused among the theatre attendants, who step forward at intervals and mop the bedewed forehead. Messrs. Smith and Nephew have kindly made this cap for me with a forehead band of a new material of an absorbent type which has a comfortable degree of elasticity and fits snugly to the forehead. If one can be sure of having one's own caps, the band is sewn the right size; if this is not so, the ends are left free and fitted with safety-pins or "rasco" clips each time the cap is used.—I am, etc.,

London, W.1. A. DICKSON WRIGHT.

POINTS FROM LETTERS

Terramycin

Dr. E. M. HAMILTON (Cranleigh) writes: I was interested to read in the *Journal* (May 10, p. 1023) of the release of "terramycin." It is almost two years since I first used this drug whilst surgeon in a well-known luxury liner. It was readily obtainable from American drug stores, but I owed my supply of this drug to the generosity of several American tourists who carried a good quantity of capsules with them as a therapeutic measure against any virus diseases they might contract during their journeys through the countries of South America, where some of the sanitation is of a very low standard. At that time terramycin cost a dollar per capsule in the United States, and this was considered very cheap by these tourists. I was also fortunate enough to have the use of streptomycin and "aureomycin" long before they became available to our hospitals at home.

Is Latin Dead?

Mr. E. WATSON-WILLIAMS (Bristol) writes: Page 1124, col. 2, third para., fourth line—"all the *meati*." Proh pudor! How are the mighty fallen. In 1905 Asquith (brother to the former Prime Minister) would have called loudly for "a basin, a basin—I am going to be sick." [We apologize to Mr. Watson-Williams and other readers for our too eager effort to keep Latin alive in last week's annotation on "Nasal Bleeding." The word should have been meatuses.—ED., *B.M.J.*]

Mr. GERALD SOLOMON (University Union, Manchester) writes: I feel that the question should be discussed as part of a far wider issue than has been considered so far by your correspondents. . . . The value of Latin lies not in "knowing" it but in studying it. The study of a language involves the study of the people who speak it or spoke it, and what medical students are most lacking in to-day is, I feel, a knowledge of people. . . . The physician or surgeon who from the age of 13 or 14 has received only a scientific education will treat cases; while his colleague who has studied, and is interested in, people, will treat people. I feel that to-day, when it is being recognized more and more that the patient and his disease are a whole, it is inconsistent not to encourage prospective medical students to study Arts at school. . . . I trust, too, that nobody will object that it is overburdening the future doctor's brain to expect him to learn and remember obscure points of the grammar of languages which he will never have need to use, unless they are willing also to relieve him of the burden of learning and remembering obscure points of the anatomy of plants and insects which he will never be called upon to treat.

Obituary

LAURENCE KILROE, M.D.

Dr. Laurence Kilroe, who died at Rochdale on May 11 at the age of 70, was a well-known and greatly respected general practitioner in the north-west of England. He was born in Bolton and educated at the University of Manchester, where he graduated M.B., Ch.B. in 1905, proceeding M.D., with commendation, in 1910. After house appointments at Ancoats Hospital and at Manchester Royal Infirmary he settled in practice at Rochdale. During the war of 1914–18 he served as a temporary captain in the R.A.M.C. and was wounded and mentioned in dispatches. He had not been well in recent months, but his death was sudden and unexpected.

We are indebted to Mr. J. C. Jefferson for the following appreciation: If conditions 40 years ago had been as they are to-day it is probable that Laurence Kilroe would have become a consultant. Whether he would have had a happier life is problematical; he would certainly not have had a more interesting or a more useful one. Possessed of a fine brain and an absolute integrity of character, he had been exceptionally well trained. He was blessed with an inquiring mind, and he had a remarkable memory, qualities which, allied with a deep interest in his fellows, ensured his success in practice. Though it came all too late, his appointment soon after the end of the last war as honorary consulting physician to Rochdale Infirmary gave him great pleasure, because it enlarged his opportunities for scientific observation.

Kilroe became widely known among his colleagues for his devoted work for the British Medical Association, to which he gave all the energies left over from his routine duties. This work ate up most of his scanty leisure. He was the mainstay of the Rochdale Division, of which he was honorary secretary for over 20 years and its representative at the Annual Representative Meeting for 16 years. He was also joint honorary secretary of the recently formed South Lancashire and East Cheshire Branch from 1950 to the time of his death, having been president of the old Lancashire and Cheshire Branch from 1939 to 1945 and chairman of the Rochdale Division in 1948–9. For some 20 years he was a member of the central ethical committee of the Association and was lecturer on medical ethics at the University of Manchester. He served on many local committees. His friends were delighted when, last year, he was elected president of the Manchester Medical Society, before which, little more than a month ago, he delivered his presidential address.

It was evidence of his exceptional activity of mind that, in spite of all his commitments, he maintained a deep interest in and enjoyment of music and literature. He was one of the most widely informed of men; there was nothing of arrogance or impatience in his composition, and his keen sense of humour made him a delightful companion. As time passed and the flesh grew weaker the spirit mellowed. The more one saw of him the more one valued him. When he gave up his insurance work he at last found sufficient time for rest and contemplation, and I am glad to think that the last few years were among the happiest of his life.

T. M. B. writes: Laurence Kilroe was a man of many activities and interests. At the top of the list came his profession, in which he was supreme as a general practitioner. As honorary physician to Rochdale Infirmary his scope became wide. He was extremely fond of music, assiduously attending the Hallé concerts in Manchester as a subscriber for nearly 50 years. Like most Irishmen, he loved a mild gamble and was never so happy as when attending a race meeting, where he met gains or losses with a gay or philosophical spirit. I was his close friend for 50 years, and as young men we often went on holiday together to the Norfolk Broads, with Dr. Hugh Ashby and the late Professor Daniel

Dougal. On those sailing days "Larry," as his friends always called him, was the cook, and a very good one too. After the war of 1914–18 the same party toured various golf courses. "Larry" was a left-hander, with an incomparable slice and an amusing habit of retreating to the far end of the tee before driving, in order to meditate. It is hard to describe a man who was so essentially lovable and such an ideal companion, by nature entirely unselfish and straightforward. He will be greatly missed by his friends.

Dr. JOHN JOSEPH KEVIN PENTONY, who died at Middlesbrough on April 4 at the age of 59, was born on July 20, 1892, and was educated at the University of Liverpool, where he graduated M.B., Ch.B. in 1915. He entered the R.A.M.C. immediately after graduation and served mainly in Sinai and in the Sahara Desert. At the end of the war of 1914–18 he was deputy assistant director of medical services. After demobilization in 1919 he joined his father, the late Dr. E. P. Pentony, who died in 1928, continuing the practice until last year. Dr. Pentony had a natural flair for organization and administration and since 1947 he had been the chairman of medical boards under the Ministry of Pensions. For a time he was honorary anaesthetist to the North Riding Infirmary, Middlesbrough. He leaves a widow and one daughter, to whom much sympathy is extended.

The sudden death of Lieutenant-Colonel JOHN HARE in London on April 16 removes from the London medical world one of its most popular members and one whose many interests outside medicine enabled him to claim friendship with people in all walks of life. John Hare was born at Wrexham in 1888, the second son of the late Mr. Samuel Hare, the well-known mining engineer, and received his medical education at the University of Durham, where he graduated M.B., B.S. in 1910. He joined the R.A.M.C. in 1912, being placed first in the entrance examination, an augury of the distinguished career which was to follow. After some years as regimental medical officer in England, Ireland, and, in 1914, in France, where he was mentioned in dispatches, he was appointed to General Hamilton's general headquarters in the Dardanelles, where his work earned him a second mention. He was then posted to East Africa, where he served with the motor ambulance convoy. At the end of the war of 1914–18 he settled down to a period of intensive study of ear, nose, and throat surgery, taking his majority examination, and being appointed ear, nose, and throat specialist to Queen Alexandra Military Hospital at Millbank in 1922, a post he held until 1939. During this period he took the F.R.F.P.S. in 1923, the D.L.O. in 1924, and proceeded M.D. in 1929. During the last ten years of this period he was also conducting a busy consulting practice. He was appointed O.B.E. in 1930 for work he did to improve the examination of the ears of Army recruits, work which involved the inspection of recruiting centres all over England and Scotland. The outbreak of war in 1939 brought about his recall to the active list, and he served as assistant director of medical services in Manchester in 1939–40, but a breakdown in health forced his retirement. Since 1941 and up to his death he had been ear, nose, and throat specialist to the Ministry of Pensions and to the London County Council, being attached to Mile End and St. George-in-the-East Hospitals. Colonel Hare had a most versatile mind and a charming personality. A musician of some brilliance, he was also a competent sportsman and artist, so that his popularity with the fellow members of his club was only to be expected. In 1919 he married Katherine, eldest daughter of the late Mr. Edward Rowe, of Capetown, and she survives him, together with two sons and one daughter. Their eldest son, a naval officer, was killed in 1941.—K. H.

Dr. CHARLES JAMES NEILAN, who died suddenly at his home at Dawdon, Seaham, Co. Durham, on April 17 at the age of 65, was born at Roscommon, Co. Connaught, on October 9, 1886, and was educated at Ushaw College, Durham, and at the University of Durham, returning to Ireland to take the L.A.H. Dublin in 1909. While at Durham he was the "Victor Ludorum" in the university sports, and he played hockey for Durham County for many years. During the war of 1914–18 he served in the R.A.M.C. in Mesopotamia. Dr. Neilan took a great interest in the work of the St. John Ambulance Brigade and was a Serving Brother of the Order of St. John of Jerusalem. He was taken seriously ill early this year but appeared to recover, and recently he had been doing a little work. He is survived by his widow, Dr. Dorothy Neilan, and one daughter.

Mr. FREDERICK LACE, who died on April 22 at the age of 88, was born at Wells, Somerset, the fifth son of the Rev. I. W. Lace, vicar of Pill, near Bristol. He received his medical training at Bristol Royal Infirmary and qualified M.R.C.S., L.R.C.P. in 1889, obtaining the F.R.C.S. six years later. After qualification he was appointed house-surgeon at the Royal United Hospital, Bath, later becoming honorary anaesthetist and assistant surgeon. From 1902 to 1922 he served the hospital as honorary surgeon, and when he retired he became honorary consulting surgeon. In 1939 he completed 50 years' service for the hospital. For many years he was honorary consulting surgeon to Chippenham Cottage Hospital and to the Eastern Dispensary, Bath, and during the war of 1914–18 he was on the staff of the Bath War Hospital. Mr. Lace was a member of the B.M.A. for 62 years, and when the British Medical Association held its annual meeting at Bath in 1925 Mr. Lace was vice-president of the Section of Surgery. For many years Mr. Lace served in the Volunteers and the Territorial Army, partly in a medical and partly in a combatant capacity, and he received the Territorial Decoration in 1914, when he retired with the rank of major. In his early years he played rugby football, and he was a prominent member of the Bristol Medical Dramatic Club and of the Bath Philatelic Society. Mr. Lace, who was a widower, is survived by two sons.

Dr. James Lindsay writes: It came as a shock to medical practitioners in the Bath and Bristol areas when it became known that Frederick Lace had passed on. He was a vigorous 88, and only a week before his death I saw him walking briskly up the rather steep Gay Street in Bath. Although it was a chilly day, he was, as usual, without an overcoat. I first came in contact with Lace in 1905. By then he had established himself as the leading surgeon in the area. Successions of house-surgeons, on coming from the great teaching hospitals, were prepared to adopt a tolerant attitude towards provincial surgeons, but they were speedily impressed by Lace's dexterity and skill. His technique was neat, and he made full use of his gift of ambidexterity. His manner might be described as being somewhat austere. Temperamentally he was shy of innovations and would be captiously critical of suggestions proffered by a new house-surgeon. Nevertheless, he quickly adopted any ideas that were good. The one man he acknowledged as an inspiring influence in his life was Greig Smith. For over 20 years Lace's life as a provincial surgeon was a record of achievement, yet throughout this period he remained in general medical practice and certainly up to a few years ago visited a few of his older patients in the capacity of family doctor. Although his working life was so fully occupied he found time to devote to gardening, freemasonry, and philately.

Dr. WILLIAM GEORGE KINGSTON, who died on April 29, was a clergyman's son, one of a family of seven. He was a student at the Middlesex Hospital, qualifying L.M.S.S.A. in 1931. In the following year he entered the R.A.M.C., but transferred to the Indian Medical Service in 1934. Ten years later he retired from the service and returned to this country, practising first at Nailsworth, in Gloucestershire, and then at Great Bedwyn, near Marlborough, where he was much loved by all his patients, whom he treated with great skill and humanity. He had a profound understanding of human nature, and was ever ready to advise on

matters outside the scope of routine medical practice. He was a good mixer and an able raconteur, with a flair for discerning the unusual in human behaviour. He was also a keen musician and an accomplished vocalist, and had broadcast on several occasions. A true *bon viveur* and connoisseur of wines, his outside interests were many. An omnivorous reader, he was well informed over a vast range of subjects. Gardening was his special hobby, and he took several prizes at shows in Gloucestershire. Always devoted to the Church, in the last year of his life Dr. Kingston gave up his leisure to the study of theology at Brasenose College, Oxford, taking an arts degree in this subject in October last year. The enthusiasm with which he embarked on this new work was characteristic. It was his intention to settle as pastor in a small village and to afford spiritual comfort as well as free medical care to the community, a plan which was frustrated by his early death. Dr. Kingston was very happy in his married life, being nobly supported by his wife. The death of this skilful and popular practitioner is a great loss to the profession and a grievous blow to his many friends and patients.

Dr. PETER ALEXANDER STEVEN, who died suddenly at his home at Ripon on April 29 at the age of 74, was born on May 2, 1877, and was educated at the University of Glasgow, where he graduated M.B., Ch.B. in 1899. After holding house appointments at Glasgow Western Infirmary and at the Glasgow Royal Maternity and Women's Hospital he worked as an assistant in general practice until he finally settled in Ripon in 1906. He was a member of the staff of the local hospital from the early days when it was a cottage hospital, and he took an active part in its development into the well-equipped Ripon and District Hospital of the present day. During the war of 1914–18 he served in the R.A.M.C., mostly in Salonika. Dr. Steven, who was at work until the day of his death, will be greatly missed by a wide circle of friends and patients. His wife, who predeceased him, was Mayor of Ripon at the time of her death in 1941. Dr. Steven leaves a son and a daughter, to whom we extend our sympathy.

Medical Notes in Parliament

HEALTH BILL IN FINAL STAGES

On May 20, when the Report Stage of the National Health Service Bill was taken in the House of Lords, Lord WOOLTON said the Government had decided that it would be right and proper only to charge out-patients for appliances which were prescribed on or after the commencement of the Act, and this change could be made in regulations under Clause 1 of the Bill.

Lord AMMON moved to exempt from charge the supply of any drug or medicine for treatment of the chronic sick, including those with malignant disease, tuberculosis, or diabetes, or in a chest clinic or other treatment centre administered as part of the hospital service.

Lord WOOLTON said the Bill affected only a small proportion of the people who suffered from the diseases mentioned. There was no equity in making a distinction between people who went as out-patients to hospitals and people who were treated by their general practitioner. Another difficulty was to arrive at the meaning of the term "chronic sick." Besides consulting the Minister of Health and his officials he had taken external advice from medical friends, and the conclusion he drew was that the Health Scheme must be preserved but that there was a danger that its growing expense might become a burden to its efficiency.

The proposed amendment was defeated by 25 to 8.

After Lord LISTOWEL'S amendment to exempt certain persons in welfare homes from charges had been withdrawn, to conclude the Report Stage, the Bill was read a third time.

Poisonous Chemicals in Agriculture

The House of Lords on May 20 went into committee on the Agriculture (Poisonous Substances) Bill. On Clause 1 (Protection of Employees against Risk of Poisoning) the House, on the motion of Lord AMHERST OF HACKNEY, added a proviso that before regulations were made the Minister should consult organizations representing the interests concerned. Subsequent clauses up to Clause 8 were approved without discussion. On Clause 9 (Substances to Which this Act Applies) Lord DOUGLAS OF BARLOCH moved to add preparations or mixtures containing any substance which since January 1, 1935, had been publicly offered for sale for use otherwise than experimentally in agriculture. He said that as the Bill stood it applied specifically only to two classes of poisons and to no others. The dinitro compounds had been introduced as medicines in 1933. Many cases of poisoning occurred, and some deaths were reported, and from 1937 their use for medical purposes had been discontinued. He hoped that other substances would not be dealt with only after such disastrous means had brought the need to notice.

Lord CARRINGTON said that at present only the dinitro and the organo-phosphorus compounds involved risk of poisoning to the workers using them. No other substance—for example, D.D.T.—involved any risk to the operators. There was ample power in Clause 9 for the Minister to include any new substance which he considered might be dangerous to workers on the land.

Lord DOUGLAS OF BARLOCH said it had been found in the United States that men engaged in using D.D.T. continuously had accumulated it in their bodies to the extent of 100 parts per million. They had not died of it, but many substances were toxic only after 10 to 20 years. A classic example of that was the use of radium.

Lord CARRINGTON reaffirmed that if any new substances which might be dangerous came into general use in agriculture the Government had power under the Bill to deal with them and to protect the workers. Obviously it was the duty of the manufacturer of a new weed-killer to carry out tests and to state clearly on tins and containers what danger there was in the use of the poison. It would not be possible for the Minister of Agriculture to test every spray which had been invented. The Ministry had excellent contacts with the manufacturers of these substances and was not ignorant of what went on.

The Report Stage then concluded.

London University's Senate Challenged

Mr. ERIC FLETCHER, on May 19, moved that an Address be presented to Her Majesty praying her to withhold approval from a statute made by the Senate of the University of London on March 21, 1951, amending the statutes of the University. Under the University of London Act (1926) the constitution of the Senate was framed to ensure a balance between the elected representatives of Convocation, which was a body of some 30,000 graduates, and the heads of colleges and the teachers, representing the salaried side of the University. The Senate had power to modify the statutes of the University unless either House of Parliament objected. He asked the House to object, because there was a feeling in the University that the changes proposed were against the public interest, and because they shifted the balance of representation on the Senate. There had been a practically unanimous vote in Convocation against the proposed new statute, but a committee of the Privy Council had expressed the opinion that technically the statute was not *ultra vires*. The statute increased by five the number of heads of colleges and schools represented on the Senate, bringing their total to 18. Graduate representation, which at present was 17 in 55, would be reduced to 17 in 60. Many other colleges and schools in the University were clamouring for representation in the Senate, and if this change were made without protest it would only be the forerunner of other changes which would further shift the present balance.

Mr. H. N. LINSTEAD said that so far there had been a representation on the Senate of 17 from Convocation and 17 from the Faculties, with in addition a representation of 13 from the schools and eight *ex-officio* and co-opted members. No one would say that the new composition of the Senate cut across the recommendation made in the Hilton Young Report of generous representation for the schools. The proposal had been thoroughly thrashed out within the University, and only Convocation had opposed the change.

Mr. SOMERVILLE HASTINGS said the University of London spent about £6m. a year on teaching, 70% or 80% of the money being derived from public sources. He submitted that to allow two out of three representatives to be teachers or representatives of the schools did not allow sufficient representation of the public. To increase these representatives but not to increase the representatives of the public through the graduates of the University would be unwise.

Mr. HENRY BROOKE, who said he was the only member of a governing body of the University of London who happened to be also a member of the House of Commons, contended there was greater representation of the public in the Senate of London than existed in any other English university.

More Medical Representatives on the Senate

Mr. J. A. BOYD-CARPENTER said the point under discussion was whether the representatives of institutions of which the University was in a sense a federation should be increased from 13 to 18 by adding one representative each for the British Postgraduate Medical Association, the School of Oriental and African Studies, and the Wye Agricultural College, and by adding two members to the existing two who represented the 13 medical schools in the University. It was no part of his duty to indicate any view on the merits of the matter.

Mr. G. R. CHETWYND suggested that the House should accept the prayer against the statute and refer the question back to the Senate so that it could work out a method of including the schools on some representative basis.

The House then agreed to Mr. Eric Fletcher's motion, which was ordered to be presented to Her Majesty by Members who are Privy Councillors or members of Her Majesty's Household.

The G.P.s' Pay

Dr. A. D. D. BROUGHTON asked the Minister of Health whether he would publish as a White Paper the terms of reference and the recommendations of the working party appointed to consider a new policy for payment out of the central pool of general medical practitioners; and if he would include therein statistics illustrating the distribution of the pool at the time of the Danckwerts adjudication.

Mr. I. MACLEOD replied that he would consider how this information could best be made available to Parliament.

Cost of Staffing Hospitals

Mr. JOHN MORRISON inquired why the salaries and wages of other staff made a greater addition to the national average cost of maintaining a patient in a general hospital than the salaries and wages of the medical or of the nursing staff, respectively.

Mr. I. MACLEOD replied on May 16 that "other staff" covered a large variety of grades, such as staff engaged on the maintenance of plant and buildings, laundries, farms and gardens, administrative, clerical, professional and technical staff, ward orderlies and ward maids, kitchen staff, and porters. The total of the salaries and wages paid to them was greater than the total salaries paid to either doctors or nurses.

Clean Food

Sir RALPH GLYN, on May 21, asked the Minister of Food to consult the Medical Research Council and ascertain to what extent illness might be caused by the insanitary conditions under which some foodstuffs were retailed to the public.

Major LLOYD GEORGE replied that the aetiology of food-poisoning was fairly well known and research was continuing. His department consulted both the Health Departments and the Public Health Laboratory Service, which was administered by the Medical Research Council, whenever occasion arose. Statutory requirements relating to the conditions in which foodstuffs were retailed had been strengthened since 1939, and no regulations about the cleanliness of food had lapsed.

Cornea Grafting Bill

On May 21 the Bill was read a second time, passed through committee and read a third time, all without debate. The Bill was read a first time in the House of Lords on May 22.

Health Service Reciprocal Arrangements

Sir IAN FRASER asked on May 22 what negotiations were proceeding with foreign, Dominion, or Colonial Governments with a view to securing reciprocal arrangements for free medical, dental, and other services for visitors or citizens settling in countries other than their own. Mr. IAIN MACLEOD replied that no negotiations were proceeding for securing general reciprocity. Discussions were being held in the Council of Europe about the medical care of persons without sufficient resources. Bilateral agreements were being negotiated with the Federal Republic of Germany, the Netherlands, Belgium, and Luxembourg about insured workers working abroad.

National Insurance Committee

Mr. R. H. TURTON stated on May 22 that matters referred to the National Insurance Advisory Committee included questions connected with the adjustment in certain circumstances of benefits paid to persons receiving free in-patient treatment in hospitals, and draft regulations relating to maternity benefits in respect of confinements abroad.[1]

Medico-Legal

BEQUESTS TO NATIONALIZED HOSPITALS

Complex Problems

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

As Mr. Justice Harman observed in 1949, bequests of legacies or shares of residue in favour of hospitals are, or were until the springs of charity were dried by crippling taxation, the commonest form of charitable bounty. It is a form of bounty in which members of the medical profession and of their families, bound by ties of affection to the hospitals in which they had their training in youth or to which they have given a life of service, are very often minded to indulge. Although it is a form of bounty which in 1946 Mr. Bevan expected to die when the National Health Service got under way,[1] no doubt because he was confident that the beneficent State would provide whatever hospitals thereafter might need, those who work in the hospitals or on the boards which administer them may have come now to think that Mr. Bevan was over-sanguine, and that there is still room for private charity to help. The publicity given to recent directions that hospital expenditure must be reduced will have given the public an opportunity to think the same.

The provisions of the National Health Service Act, 1946, which bear on this problem are of some complexity. Fortunately for them, executors of wills who find it difficult to decide what they should do with the testator's money because the dispositions in his will are fraught with legal complication can go to the High Court for the directions of a Judge of the Chancery Division, and so conclusively protect themselves from doing the wrong thing. Since 1949 the Law Reports record no fewer than eight occasions on which executors of wills making gifts to hospitals have done so.

[1] *Hansard*, May 23, 1946, p. 271.
[2] *British Medical Journal*, March 10, 1951, p. 533.

That the executors have not done so unnecessarily is shown by the fact that on two of these occasions an appeal was brought against the decision of the Chancery Judge, and on each the Court of Appeal decided that his appreciation of what the Act meant and of what effect it had was wrong.

Illustrative Cases

By her will dated June 18, 1948, Mrs. Kellner left one-eighth of her residue to the Royal Cancer Hospital, and a further eighth to the Cancer Research Institute. She died on June 23, but probate of the will was not granted till after the appointed day for the National Health Service Act. Mr. Justice Harman came to the conclusion that her gifts were not covered by the vesting provisions of the Act and should therefore be administered charitably by the Crown under the Sign Manual. The Court of Appeal, however, decided that Section 60 of the Act did apply, and that the trustees should pay the bequest to the board of governors constituted by the Act to control both the hospital and the institute as a designated teaching hospital.

By her will dated August 9, 1944, Mrs. Morgan left the bulk of her residue on trust for the Liskeard Cottage Hospital. She died after the appointed day, when the governing body of the hospital dissolved and its property vested under the Act in the Plymouth, South Devon, and East Cornwall Hospital Management Committee. Mr. Justice Roxburgh ordered that the legacy should be paid to the committee to be applied by it only for the purposes of the Liskeard Cottage Hospital, and not for the many others controlled by the committee. Soon afterwards Mr. Justice Vaisey followed this decision in a case where Thomas Wentworth Glass had left a legacy of £250 to the King Edward VII Memorial Hospital, Ealing. Under the Act this hospital became managed and controlled, together with many other hospitals, by the South-west Middlesex Hospital Management Committee. Mr. Justice Vaisey made a similar decision where William Turner Hunter, who died in January, 1948, had left part of his residue in memory of his father to the trustees of the Ingham Infirmary and South Shields and Westoe Dispensary, which under the Act came, together with many other hospitals, under the management and control of the South Shields District Hospital Management Committee.

A different problem arose under the will of Mrs. Ginger, who in 1940 left £1,000 for the foundation of a cot at the Westminster Hospital in memory of an uncle. Under a 1940 scheme founders of cots had the right, among other things, to nominate patients, subject to certain conditions, to occupy them. This right no longer existed under the Act. Mr. Justice Roxburgh decided that the £1,000 should be paid to the board of governors of the hospital on their undertaking to name a cot in perpetuity in memory of the uncle.

The problem caused by the will of Mr. Meyers was that he left legacies to a large number of hospitals, some incorporated and some unincorporated, some of which were designated as teaching hospitals under the Act and some not, directing that they were to be treated as capital and to be added to the invested funds of the charities to which they were given. As a result of the Act all the hospitals' property had vested either in regional boards or in boards of governors, and they no longer had any invested funds. Mr. Justice Harman decided that the legacies were none the less payable to the appropriate boards of governors in the case of the teaching hospitals, and to the appropriate management committees, with directions that, as in Mrs. Morgan's case, they should use them only for the purposes of the named hospital Mr. Meyers had intended.

Attempts to Provide for Nationalization

Finally, there were two cases in which there was the added complication that the testator had foreseen and tried to provide for what was to happen if the hospital concerned was nationalized. John Edward Frere, by testamentary dispositions made on or before 1941, left £6,300 to Fleet and District Hospital if still at his death "run on a voluntary system and not taken over by the State." He also left his residue to the same hospital. He died in 1949. Mr. Justice Wynn Parry held that the £6,300 legacy lapsed because the hospital was "taken over by the State" under the Act, but that, as Mr. Frere had failed to make a similar restriction when leaving his residue to the same hospital, the residue must be paid to the Farnham Group Hospital Management Committee.

By her will dated January 13, 1943, Lady Bland-Sutton, widow of Sir John Bland-Sutton, left her residuary estate to trustees on trust to provide annually for a research scholarship and then to pay the residual income to the treasurer of the Middlesex Hospital for the maintenance and benefit of the Bland-Sutton Institute of Pathology, which was part of the Medical School.[2] If the Middlesex Hospital became nationalized or passed into public ownership the trustees were to pay both capital and income to the Royal College of Surgeons. The Court of Appeal decided that the effect of the Act had been that the Middlesex Hospital had become nationalized and had passed into public ownership within the meaning of Lady Bland-Sutton's will. The Court further held that the Royal College of Surgeons was not a charity within the meaning of the Statute of Elizabeth. Therefore, as the date on which "nationalization" of the hospital might take place was wholly uncertain at the date of Lady Bland-Sutton's death in 1943, the gift over to the College was void as offending against the "Rule against Perpetuities." The Court held, however, that the charitable intention behind the gift to the Institute transcended the restriction that the gift should not go to the Institute in case of the nationalization of the hospital, and that this restriction must therefore be disregarded rather than allow the gift to fail completely.

Getting the Courts to say what testators mean is an expensive matter. The pitfalls which may beset legacies to hospitals since the National Health Service began have undoubtedly not yet been fully explored. Those who have indulged or are minded to indulge in this form of bounty should be warned by these illustrations to get professional help to see that it goes where they mean that it should go.

Universities and Colleges

UNIVERSITY OF OXFORD

In a Congregation held on May 1 the degree of D.M. was conferred on I. V. Polunin.

UNIVERSITY OF CAMBRIDGE

In Congregation on May 10 the following medical degrees were conferred:

M.D.—R. S. Stevens, J. H. Simpson, P. G. Mann, R. H. Ellis, J. F. Buchan.

M.B., B.CHIR.—D. W. Hall.

UNIVERSITY OF EDINBURGH

Dr. A. A. B. Swan has been appointed lecturer in the department of physiology, from October 1, and Dr. B. McL. More, assistant lecturer, from April 21.

The status of honorary lecturer in the department of tuberculosis has been granted to Dr. N. W. Horne.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College, held on May 6, with the President, Dr. W. A. Alexander, in the chair, the following were elected Fellows of the College: R. F. Robertson, J. T. R. Russell.

The following were elected Members of the College: G. B. Sinha, S. Balse, S. H. Shah, G. F. Hall, M. J. Bailey, S. Ruttle, D. P. Basu, B. S. Kulkarni, N. M. Mann, D. T. Kay, O. G. Jones, W. Bolliger, A. Macfarlane, N. K. Pein, W. I. Forsythe, W. D. H. Conacher, A. D. Desai, Z. H. N. Kadri, S. N. Mathur, R. A. Kershaw, B. Prasad, G. S. Kilpatrick, R. J. Connolly, K. L. Stuart, J. A. McLeod, B. S. Khaira.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **May 10** (No. 19) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire.	1951 Eire
Diphtheria	16	3	10	0		38	3	18	1	0
Dysentery	367	34	61	5	1	940	196	151	19	3
Encephalitis, acute	5	0	1	0		2	0	0	0	
Enteric fever: Typhoid	3	0	0	0	1	3	1	0	0	2
Paratyphoid	5	0	8(B)	0		10	0	0	0	
Food-poisoning	91	4		0		107	11		0	
Infective enteritis or diarrhoea under 2 years				12	23				17	22
Measles*	4,494	240	426	228	469	19,929	881	494	284	182
Meningococcal infection	40	3	14	0	2	33	2	24	0	
Ophthalmia neonatorum	36	1	13	0		32	4	7	0	
Pneumonia†	491	34	214	6	2	574	36	169	8	1
Poliomyelitis, acute: Paralytic	15	3	5	1		11	1	1	1	1
Non-paralytic	6	0				10	0			
Puerperal fever‡	267	41	17	2	1	78	10	8	0	1
Scarlet fever	1,033	74	172	20	61	1,025	66	129	30	57
Tuberculosis: Respiratory			153	24				202	46	
Non-respiratory			24	8				33	4	
Whooping-cough	2,993	178	191	79	61	3,206	161	469	48	51

DEATHS in Great Towns	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire.	1951 Eire
Diphtheria	0	0		0	0	*0*	0	*0*	0	0
Dysentery	3	1		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0		0		*0*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	10		4	1	1	*6*		*2*	2	2
Influenza	9	1	1	0	0	*15*	3	*0*	0	1
Measles		0	2	0	2		1	*0*	0	1
Meningococcal infection		0	2				0	*0*		
Pneumonia	203	28		8	5	*180*	36		4	6
Poliomyelitis, acute	1	0			0	*2*	0			0
Scarlet fever		0		0	0		0	*0*	0	0
Tuberculosis: Respiratory	113	24	23	2	8	*138*	24	*19*	7	12
Non-respiratory		1	6	0	1		3	*7*	4	3
Whooping-cough	2	1		0	0	*7*	1	*0*	0	0
Deaths 0–1 year	193	21	40	15	7	*227*	33	*37*	8	19
Deaths (excluding stillbirths)	4,790	694	591	118	151	*4,835*	794	*587*	111	174
LIVE BIRTHS	8,145	1212	937	247	450	*7,721*	1272	*989*	233	412
STILLBIRTHS	199	26	28			*188*	24	*24*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
‡ Includes puerperal pyrexia.

Vital Statistics

Infectious Diseases

An increase was recorded in the number of notifications of scarlet fever 156 and dysentery 126 in England and Wales during the week ending May 10, while decreases were reported for measles 249, whooping-cough 110, and acute pneumonia 91.

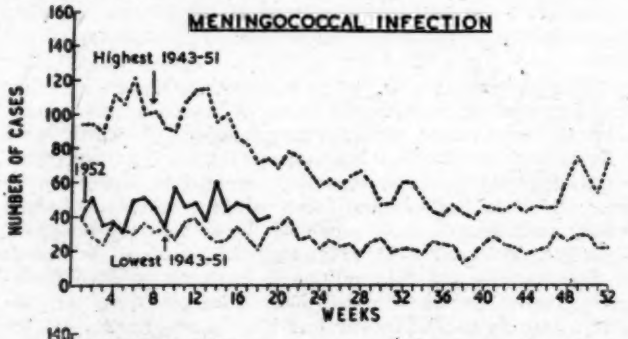
A small increase occurred in the incidence of scarlet fever in every region except the south-east. The decrease in the incidence of measles was due to the experience of the Midlands and north-western region; in every other region a small rise occurred. The largest falls in the number of notifications of measles were Lancashire 119, Lincolnshire 50, and Staffordshire 50. The largest declines in the number of notifications of whooping-cough were Yorkshire West Riding 45, Durham 38, and Kent 34, and the largest rise was Essex 33. The notifications of diphtheria were 5 fewer than in the preceding week; the total was the lowest ever recorded in this country, being 3 below the previous lowest level. The only administration areas with two cases of diphtheria were Liverpool C.B. and Heston and Isleworth M.B.

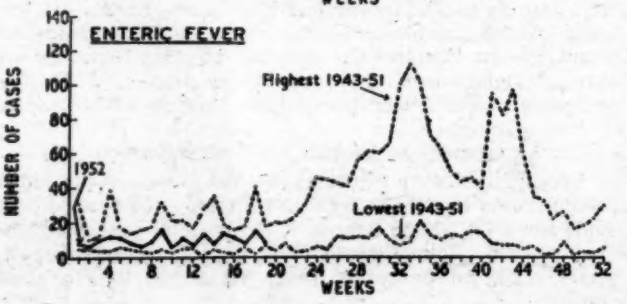
The number of notifications of acute poliomyelitis was 3 fewer for non-paralytic but the same for paralytic cases as in the preceding week. The largest returns during the week were Sussex 5 (Brighton C.B. 3) and London 3.

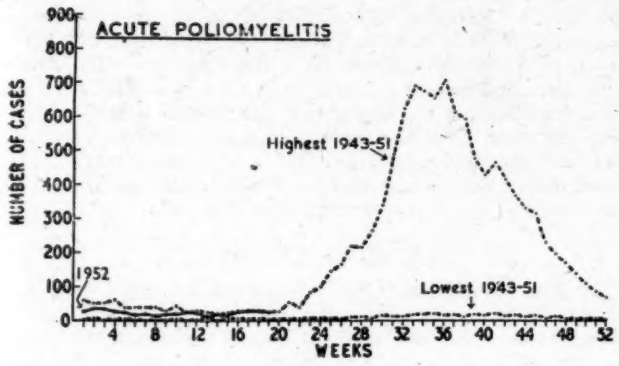
The chief feature of the returns of dysentery was a large increase in Lancashire, where the notifications rose from 37 to 167. The largest centres of infection in this county were Preston R.D. 45, Manchester C.B. 23, Swinton and Pendlebury M.B. 18, Liverpool C.B. 17, Whiston R.D. 14, Clitheroe R.D. 11, and Warrington R.D. 10. A further 17 cases were notified from the outbreak in Berkshire, Maidenhead M.B., where 16 cases occurred last week. The other large returns were London 34 (Wandsworth 12), Yorkshire West Riding 25 (Huddersfield C.B. 11), and Middlesex 25.

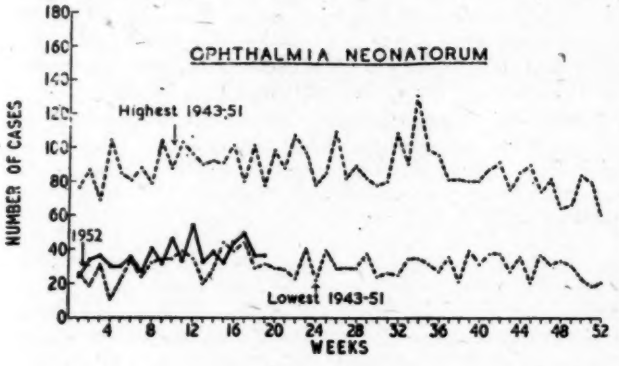
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1943–51 are shown thus -------, the figures for 1952 thus ————. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending May 17

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,088, whooping-cough 2,905, diphtheria 27, measles 5,749, acute pneumonia 432, acute poliomyelitis 37, dysentery 328, paratyphoid fever 22, and typhoid fever 1.

Skin Rash at Cheltenham

The outbreak of a puzzling rash at Cheltenham was reported in these columns on February 23 (p. 444), and a brief clinical description was given. Dr. R. Bowers has read a short paper on the epidemic to the Section of Dermatology of the Royal Society of Medicine, which is to be published in the *Proceedings*. He believes the condition to be the same as one described as epidemic folliculitis, a six-months outbreak of which occurred in Switzerland in 1944 (R. Schuppli, *Dermatologica*, 1947, **94**, 50).

We are indebted to Dr. Donald E. Morley, medical officer of health for Cheltenham, for the following information.

Strong evidence indicates that the use of water from a single open reservoir was associated with the outbreak. It was in use for three periods this year and was last in use in August, 1951. Information about the dates of onset of the rash in the first wave of cases was not very accurate, but the use of water from the reservoir corresponded roughly with the occurrence of cases. In a second wave of 55 cases the dates of onset were known accurately. It was found that they began on the day after the reservoir had been put into supply. The last case in that wave was reported on the day after the supply was cut off. A third wave of a few cases again occurred when the water was in use.

All supplies entering the reservoir are chlorinated, and it is not considered that bacterial contamination caused the outbreak. Biological examination of the reservoir showed a somewhat varied content of animal and plant life, but nothing unexpected. There is evidence that the condition is not infectious.

Medical News

Third Impression of "Any Questions?"—In response to a very keen demand a third impression of the book *Any Questions?* has now been printed. Copies will be available next week, and those wishing to obtain one should order without delay—price 7s. 6d. (postage 6d.)—from the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1. Although specially intended for general practitioners, the book has also been found useful by consultants whose interests are wider than their own specialty, and by students.

Hunterian Society's Essay Competition.—The subject for the 1952 gold medal essay is "The Management of Hypertension in General Practice." The competition is open to all general practitioners. Further details may be had from the honorary secretary, Mr. Alec W. Badenoch, 110, Harley Street, London, W.1.

The Joint Tuberculosis Council.—The annual luncheon was held at the National Liberal Club on May 17 with Dr. Peter Edwards in the chair. More than one of the speakers referred to the independence of the council, whose members represented all the organizations and associations which were concerned in some way or other with tuberculosis. The toast to the Joint Tuberculosis Council was proposed by Dr. A. Sandison, formerly of the Ministry of Pensions. In an interesting survey of the history of the council he dwelt particularly on the invaluable work of its founder, the late Dr. Edward Ward. Dr. Peter Edwards, who also referred to the pioneering days of 1911, mentioned the advantages that accrued from the presence of observers from Government departments at the meetings of the council. The health of the guests was proposed by Professor F. R. G. Heaf, who gave a special welcome to Dr. Dudley Irwin, of Pittsburg, and to Dr. James Watt, a past president. Mr. G. L. C. Elliston, secretary of the Society of Medical Officers of Health and Editor of *Public Health*, made a short and felicitous reply.

North of England Obstetrical and Gynaecological Society.—A meeting was held in Sheffield on Friday, April 25, with the president, Mr. P. Malpas, in the chair. Mr. G. W. Blomfield demonstrated a 2,000,000-volt *x*-ray therapy unit and gave a preliminary report on its use in gynaecology. Dr. C. J. Dewhurst described four cases of kyphoscoliosis complicating pregnancy and labour, and Professor C. Scott Russell described two cases of pseudomyxoma peritonei and showed a film.

Another Popular Health Magazine.—*Your Health* is the name of the new health magazine for everyone published by the Indian Medical Association. The foreword to the first issue, which came out in January, explains that the aim of the I.M.A. in starting it was to "impart the much-needed health education to the common people" of India. Judging by the high standard of the first issue it seems very likely they will succeed in this endeavour, especially if, as they hope, they can in time publish *Your Health* in the national languages as well as English. An attractive front cover, and good, reliable, but certainly not boring or difficult information and advice inside, make this magazine well worth the 12 annas (1s. 2d.) it costs. Our feeling that it could with advantage have more illustrations is in fact the only criticism we have to offer. *Your Health* is published from the I.M.A., 23 Samavaya Mansions, Corporation Place, Calcutta 13.

International Fertility Association Formed.—In Rio de Janeiro on October 18, 1951, delegates from 12 nations founded a new world medical society known as the International Fertility Association. The aims of this organization are to study the problems of fertility and sterility in

their broad implications; to stimulate scientific investigation and social awareness in the field of fertility and sterility; to standardize and orient nomenclature, terminology, tests, and evaluation of diagnostic methods and therapy throughout the world; and to hold international congresses. The first one sponsored by the new society will be held in New York City in May, 1953, in conjunction with the American Society for the Study of Sterility. Further information will be given by Dr. Abner I. Weisman, associate secretary-general, 1160, Fifth Avenue, New York, N.Y.

Nutrition Society.—The following changes in the officers of the society were made at the annual general meeting on May 15: Treasurer, Dr. A. J. Amos, The Laboratories, Dudden Hill Lane, Willesden, N.W.10 (GLAdstone 0665); Programmes Secretary, Dr. R. J. Allen, Monkhouse and Glasscock, Ltd., Snowsfields, London, S.E.1 (HOP 4321); Secretary, Dr. G. H. Bourne, London Hospital Medical College, Turner Street, E.1 (BIShopsgate 9936).

Society for General Microbiology.—The treasurer is Dr. R. Lovell, Vine Cottage, Streatley-on-Thames, Berks. The names of the other officers were given on May 17, p. 1090.

Abstracts of World Medicine and World Surgery.—Changes are announced in the editorship, frequency of publication, and future of the two abstracting journals published by the British Medical Association. Dr. D. I. Crowther succeeds the late Dr. G. M. Findlay as editor, and as the journals have recently fallen behind their monthly schedules the March and April numbers have been issued together for each journal, as will be the May and June numbers. *Abstracts of World Surgery, Obstetrics, and Gynaecology* will cease to appear after June, but surgical items will find a place in the remodelled *Abstracts of World Medicine*, which will appear in July and every month thereafter. No change of subscription is planned. Those who have ordered the surgical abstracts will receive instead the remodelled medical abstracts after June, unless they ask for the return of the balance of their subscription. A notice to this effect appears in the March-April issue of both sets of abstracts. It is hoped that the one abstracting journal—*Abstracts of World Medicine*—will have a wider appeal than formerly, especially to clinical workers. The changes envisaged in it will be effected gradually over the second six months of this year. It can be obtained on application to the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, at an annual subscription of £4 4s.

Fifth World Health Assembly Ends.—In a spirit of conciliation and harmony, and in order to avoid any possible prejudice to the World Health Organization, the Committee on Programme and Budget concluded its long debate on the population problem on May 19, noted the views expressed, and decided that no further action was indicated. This solution to the problem was suggested by the delegate for Ceylon, supported by the United States representative. All three resolutions before the Committee were withdrawn. The first had requested the Executive Board to establish an expert committee to examine and report on medical and socio-medical aspects of the population problem; the second, sponsored by the delegations of Belgium, Italy, and Lebanon, was to the effect that, from the purely medical standpoint, population problems did not require any particular action on the part of W.H.O. at the present time; and the delegate for India had introduced a third resolution requesting the Director-General and the Regional Committees, if the latter so wish, to consider the question of population problems in the light of the discussions held by the Committee on Programme and Budget, and to report at a subsequent meeting of the World Health Assembly. The Committee also recommended that W.H.O.'s 1953 budget of $8,485,095 should be divided among administrative services ($1,132,709), organizational meetings ($266,830), and operating programme ($7,085,556); and authorized the Director-General, Dr. Brock Chisholm, to extend for one year W.H.O.'s participation in the work of the U.N. Relief and Works Agency for Palestine Refugees. Dr. Chisholm, whose five-year contract with W.H.O. expires in July 1953, was unanimously asked to renew his contract for a further three years from that date. Because the construction of a new wing of the Palais des Nations at Geneva to house W.H.O. headquarters will cost more than the three million Swiss francs allotted by the Swiss government plus the one million francs provided from W.H.O.'s budget, a further sum of $129,330 was voted. The Assembly closed on May 22.

COMING EVENTS

Medical Illustration.—The Royal Photographic Society of Great Britain, in co-operation with the Medical Artists' Association, is holding an exhibition of medical illustration in the old Library, B.M.A. House, from June 14 to 28. Hours of admission will be 10 a.m. to 5 p.m. from Monday to Friday except Wednesdays, when the exhibition will remain open until 8 p.m. Admission free. On July 7 the exhibition will open in Manchester, at the University Medical School, for a fortnight until July 19.

Society for Endocrinology.—A one-day symposium on the posterior pituitary has been arranged for June 21 at Cambridge. Persons wishing to attend who are not members of the society should write to Professor N. F. Maclagan, Westminster Medical School, Horseferry Road, London, S.W.1, for further information. The officers and the committee of the society for this year are: chairman, S. J. Folley; honorary secretaries, C. H. Gray and N. F. Maclagan; honorary treasurer, F. L. Warren; editor of society's proceedings, S. Zuckerman; ordinary members of committee, E. C. Amoroso, G. W. Harris, C. J. O. R. Morris, and S. L. Simpson. Communications should be sent to the honorary secretary of the society, Department of Chemical Pathology, King's College Hospital, Denmark Hill, London, S.E.5.

Faculty of Radiologists.—The annual meeting of the Faculty will take place at the Royal Victoria Infirmary, Newcastle-upon-Tyne, on June 21 and 22. Full details of the programme may be obtained from the Faculty, 45, Lincoln's Inn Fields, London, W.C.2.

Tuberculosis Conference.—The Socialist Medical Association announces that it is holding a national tuberculosis conference in Battersea Town Hall, London, on June 28 and 29. It will be opened by Mr. Aneurin Bevan and closed by Mr. Sydney Silverman, and other speakers include Dr. H. Joules and Mr. Somerville Hastings. The problem of tuberculosis will be discussed from both medical and social angles. Further details may be had from the S.M.A., 86, Rochester Row, S.W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday, May 30

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., *"Tuberculosis and Sarcoid,"* clinical demonstration by Dr. G. B. Dowling.

Monday, June 2

EDINBURGH UNIVERSITY, University New Buildings, Teviot Place.—At Physiology Class Room, 5 p.m., *"Discoveries and Inventions,"* lecture-demonstration by Dr. Douglas Guthrie.

Tuesday, June 3

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.—5 p.m., *"Some Reflections on the Surgical Treatment of Epileptic Patients,"* by Dr. S. Obrador Alcade (Madrid).

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, Ducane Road, London, W., 3 p.m., *"Breech Presentation,"* by Mr. K. Vartan.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, Keppel Street, W.C., 5.30 p.m., *"Transformation Reactions in Pneumococci,"* by Dr. C. M. Macleod.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School, London, W.—5 p.m., *"Diphtheria. Beware!"* by Dr. W. H. Bradley.

Wednesday, June 4

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—11.45 a.m., medical clinical-pathological conference.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—5.30 p.m., *"The Eye as an Optical System,"* by Mr. J. F. P. Deller.

Thursday, June 5

EDINBURGH UNIVERSITY, University New Buildings, Teviot Place.—(1) 5 p.m., *"Paediatric Pseudopodia,"* Honyman Gillespie Lecture by Professor W. S. Craig. (2) At Physiology Class Room, 5 p.m., *"Eighteenth Century Surgery and Obstetrics,"* lecture-demonstration by Dr. Douglas Guthrie.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—4 p.m., *"Cutaneous Allergy,"* by Dr. Stephen Gold.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—3.45 p.m., *"Argentaffinomata of the Alimentary Canal,"* Erasmus Wilson Demonstration by Mr. E. W. Grahame.

ST. ANDREWS UNIVERSITY.—At Materia Medica Department, Medical School, Small's Wynd, Dundee, 5 p.m., *"The Synovial Joint. Some of its Anatomical and Physiological Problems,"* by Professor D. V. Davies.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—5 p.m., lecture-demonstration in psychiatry by Sir Paul Mallinson.

Friday, June 6

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., *"Reticuloses,"* clinical demonstration by Dr. B. Russell.

OXFORD UNIVERSITY.—At Maternity Lecture Theatre, Radcliffe Infirmary, 2.30 p.m., *"Antibiotic Synergism and Antagonism,"* by Dr. E. Jawetz (California).

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—11.15 a.m., surgical clinical-pathological conference; 2 p.m., *"Crohn's Disease,"* by Mr. Harold Edwards; 4 p.m., *"Cutaneous Allergy,"* by Dr. Stephen Gold.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—4.30 p.m., *"Surgery of Lacrimal Sac and Ducts,"* by Mr. A. J. Cameron.

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY, Whipps Cross Hospital, London, E.—8.30 p.m., *"The Changing Face of Therapeutics,"* by Dr. C. A. Keele.

APPOINTMENTS

BRACKENRIDGE, GILBERT R., M.B., Ch.B., Senior House Officer (Medicine), Victoria Hospital, Blackpool.

GRAY, S. T. G., M.B., Ch.B., D.P.H., County Medical Officer of Health and School Medical Officer, East Suffolk County Council.

JAMES, S. G., M.D., M.R.C.P., D.P.M., Medical Superintendent, Broadmoor Institution.

JEREMIAH, C. W. W., M.R.C.S., L.R.C.P., D.P.H., County Medical Officer, Nottinghamshire.

MARTIN, M. P. D., M.B., Ch.B., Assistant Chest Physician (S.H.M.O.) for Montgomery and Merionethshire.

NORTH-EAST METROPOLITAN REGIONAL HOSPITAL BOARD.—*Part-time Consultant Physician, Tilbury and Riverside Hospitals (Tilbury and Orsett Branches),* I. M. Hall, M.D., M.R.C.P. *Part-time Consultant Physician in Physical Medicine, St. Mary's, Colchester, and other Hospitals in the Group,* K. W. Nicholls Palmer, L.M.S.S.A., D.Phys.Med. *Part-time Consultant Physician in Physical Medicine, North Middlesex Hospital and Annexes,* J. F. Dignan, M.B., B.Ch., F.R.C.S.I., D.Phys.Med. *Part-time Consultant Dermatologist, Prince of Wales's General Hospital,* L. Sefton, M.B., B.Chir., M.R.C.P. *Part-time Consultant Radiologist, Forest Hospital,* M. I. Robinson, M.B., B.Ch., D.M.R.D. *Part-time Consultant Radiologist,* Mildmay Mission, Plaistow and Claybury Hospitals, C. J. R. Morrison, L.R.C.P.&S.Ed., D.M.R.D.

RANGER, DOUGLAS, M.B., B.S., F.R.C.S., Assistant Laryngologist (Consultant), London Chest Hospital.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—*Psychiatric Registrars to South-western Region,* E. G. W. Cross, M.R.C.S., L.R.C.P., N. Lukianowicz, M.D., and A. W. Taylor, M.B., B.S. *Senior Registrar in Orthopaedic and Traumatic Surgery to Bath Clinical Area,* P. S. London, M.B., B.S., F.R.C.S.

THOMSON, G. RUSSELL, M.B., Ch.B., F.R.F.P.S., F.R.C.S.Ed., Consultant Surgeon and Medical Superintendent, West Highland Hospital, Oban, Argyll.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Patey.—On May 17, 1952, at the Hill Nursing Home, Reading, Berks, to Elaine, wife of Dr. George Patey, a son.

DEATHS

Adams.—On May 19, 1952, at 1, Chapel Road, West Ealing, London, W., Percy Edward Adams, M.D.

Daunt.—On May 18, 1952 at 74, Filsham Road, St. Leonards-on-Sea, Sussex, Francis Eldon Daunt M.B., B.S.

Dutton.—On May 18, 1952 at 26, Poplar Grove, Stepping Hill, near Stockport, Cheshire, Edward Charles Dutton, M.B., F.R.C.S.Ed., aged 76.

Harbinson.—On May 16, 1952 at "Dunimarle," Revidge Road, Blackburn, Lancs, Josiah Stranaghan Harbinson, M.B., Ch.B., J.P.

Ibbotson.—On May 20, 1952 at the Royal Northern Hospital, Holloway, London, N., William Ibbotson, F.R.C.S.Ed., late of 78, Harley Street, London, W., aged 74.

Morrin.—On May 19, 1952, at his home, 1, Walton Place, London, S.W., John Joseph Morrin, M.B., B.Ch.

Any Questions ?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Digitalis in Toxic Myocarditis

Q.—*What are the present views on the use of digitalis or its derivatives in heart failure concurrent with and following acute toxaemic states—e.g., influenzal bronchopneumonia? Is its cautious administration while awaiting the full effect of antibiotics very dangerous?*

A.—Digitalis is of value in all forms of congestive heart failure whatever the cause and whether the rhythm is normal or otherwise. Heart failure from toxic myocarditis is no exception, and such toxic myocarditis is not influenced by antibiotics, being probably allergic in nature. There is no object in giving digitalis to prevent the development of heart failure in any infection, the incidence of toxic myocarditis being very low and digitalis doing more harm than good in the absence of congestive failure. The drug may also be used to control the ventricular rate in auricular fibrillation or flutter complicating pneumonia or other infections, but its use does not prevent the onset of such rhythm changes, nor does it influence sinus tachycardia.

Discoloration of Penicillin in Syringes

Q.—*Is an all-glass syringe essential when giving penicillin preparations in oil? I notice that when using a syringe with a metal plunger the contents of the syringe are often discoloured, and wonder how much this is likely to affect the potency of the penicillin? What is the cause of the discoloration?*

A.—A slight degree of degradation of penicillin takes place in such preparations, and the sulphur so liberated combines with the metal of the syringe to form a sulphide, to which the discoloration is due. It is only noticeable because the oil suspension affords a white background: the same change in a syringe containing an ordinary solution of penicillin would pass unobserved. There is thus no effect on the potency of the preparation, the change to which the reaction is due having taken place before the syringe is filled.

Potassium Depletion in Cushing's Syndrome

Q.—*Would you let me know why in Cushing's syndrome a hypochloraemic hypokalaemic alkalosis may be found?*

A.—In some cases of Cushing's syndrome there is excessive production of adrenal steroids with an action similar to that of synthetic desoxycorticosterone, in that they increase the urinary output of potassium. In such cases considerable potassium depletion is produced; and in them alkalosis may be present. The alkalosis responds to treatment with potassium salts, and alkalosis has been found in experimental potassium depletion in animals and man. It seems reasonable therefore to relate the alkalosis of Cushing's syndrome to potassium depletion. There is evidence that even in potassium depletion alkalosis does not occur if the diet is of low salt content; variation in potassium and sodium intake, as well as in the type of steroids produced, may thus explain the inconstancy of alkalosis in Cushing's syndrome. When alkalosis does occur, it should be treated by giving 10 g. of potassium chloride daily by mouth, in divided doses, until the alkalosis is controlled.

Oral Cortisone for Asthma

Q.—*Is oral cortisone useful in the treatment of chronic asthma? If so, what dosage is recommended?*

A.—Cortisone by mouth usually has a beneficial effect in chronic asthma, but relief is likely to continue only while the cortisone is being given. The dosage suggested is 100 mg. to 300 mg. daily until marked or maximum improvement occurs (24 hours to four to five days, or possibly a little more depending on the dose used), and then as small a dose as is consistent with a maximum of relief and the minimum risk of side-effects. It is wise to exclude any asthmatic who happens also to have a peptic ulcer, tuberculosis, diabetes, hypertension, coronary artery disease, a psychopathic personality, congestive heart failure, haemorrhagic tendencies, or who is pregnant. The present shortage of supplies of cortisone and the possible need for continuing treatment if obviously beneficial results are obtained should be considered *before* starting any chronic asthmatic on this treatment. Prolonged treatment with cortisone in asthmatic patients raises questions which cannot yet be answered.

Pregnenolone and Arthritis

Q.—*Does pregnenolone benefit any variety of arthritis? It has been suggested for the treatment of a case of osteo-arthritis. If indicated, what is the dosage, and for how long should it be given?*

A.—Although it has been claimed in certain clinics in America that pregnenolone has a beneficial effect in rheumatoid arthritis, trials in other clinics on both sides of the Atlantic have failed to substantiate these claims. On present evidence pregnenolone is not indicated in any form of arthritis.

Keratoderma Climactericum

Q.—*What are the likely causes of recent gross thickening and fissuring of the feet, especially around the ends of the first toes and the heels, in a woman of 48? There is a past history of chilblains on the feet for a number of years. What treatment is advised, and is there any danger of malignant change?*

A.—It seems likely that this is an early or mild case of keratoderma climactericum. This disorder, described by Haxthausen, is characterized by patchy hyperkeratoses of the soles, particularly at the sites mentioned in the question. It appears after the menopause, and is often associated with obesity, hyperpiesis, and arthritis, particularly of the knees. Possible alternatives are hyperkeratotic eczema, psoriasis, or ringworm infection. Keratoderma climactericum does not usually respond very well to endocrine treatment. Local treatment is symptomatic and usually best carried out by a chiropodist.

Flavine Rashes

Q.—*One of my patients has developed a severe rash following the local application of acriflavine. Please advise on treatment.*

A.—The various antiseptics of the flavine group are not particularly uncommon causes of contact sensitivity and are also known to give rise to skin eruptions when given by injection. In treating contact dermatitis due to acriflavine or proflavine the first essential is, of course, to stop the application of the disinfectant. It is as well to protect the patient from strong light, since it seems that photosensitivity is sometimes associated: occasionally a localized eruption may become generalized.

The treatment is the treatment of contact eczematous dermatitis whatever the cause: in the most acute and weeping stages calamine lotion combined, if necessary, with twice-daily soaks of potassium permanganate (1 in 8,000). In the less acutely inflamed stages zinc cream may be applied instead. The antihistamine drugs are not likely to have much effect in altering the activity of the process, but their sedative action may be helpful. Sensitivity to one member of the flavine class usually implies a group sensitivity to other acridines, so that all these antiseptics should be avoided in the future.

Heartburn

Q.—*What is the mechanism of heartburn? How should it be treated if no underlying cause can be found?*

A.—The symptom of heartburn does not, in itself, indicate organic disease. It is a burning sensation that is felt in the line of the oesophagus anywhere from the thyroid cartilage to the lower end of the sternum. It can be associated with acid eructations, but it has been reported in cases with complete achlorhydria. Oesophageal spasm has been regarded as the cause of this symptom for some time, and recently careful radiological examination has shown oesophageal reflux to be present in a very high percentage of cases. Its effect may well be to produce spasm in the early stages, but ultimately the irritation may lead to an oesophagitis or ulceration.

Posture is the most important factor in the production of heartburn. As stooping, leaning forward, and lying down produce it, bending the knees and keeping the trunk erect, sitting up at a desk as straight as possible, and sleeping with the bed-head raised are important pieces of advice. Antacids are of little value, but bismuth carbonate is sometimes helpful. Certain proprietary preparations are useful in individual cases, but the most fruitful form of treatment is advice on posture; this not infrequently results in rapid relief of symptoms.

NOTES AND COMMENTS

Aluminium and Silicosis.—Dr. P. HEFFERNAN (Cyprus) writes: May I be allowed to differ from the statement ("Any Questions?" April 12, p. 829) that "silicosis is thought to be due to the action of silicic acid [*sic*] formed by solution of silica"? This theory has long been obsolete. The modern belief is that silica dust freshly made from the crushing of silicious rock exerts its *specific* action upon the lungs because of its surface chemical activity. This surface activity derives from the peculiar atomic lattice-structure of silica and the silicates. Powdered aluminium forms a surface chemical combination with the freshly formed silica dust, and neutralizes its specific action by converting it from an active into an inert dust. Recent observers in Africa and in America, if not in Britain, stress the fact that silica dust has to be freshly generated by crushing, etc., if it is to cause specific silicosis. Any inert mineral dust, including *stale* silica dust, can bring about generalized pneumoconiosis.

OUR EXPERT writes: Dr. Heffernan is quite right in suggesting that we do not know how silica reacts on the tissues. The chemical theory is one which has certain disadvantages, but it still remains quite a useful working hypothesis. Whether or not the alternative hypothesis is actually better I do not know, but it does not make much practical difference so far as the question to which I was replying is concerned. The freshly fractured surface theory of silicosis has been reviewed by B. M. Wright (*Nature*, 1950, **166**, 538) and is considered untenable.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.